



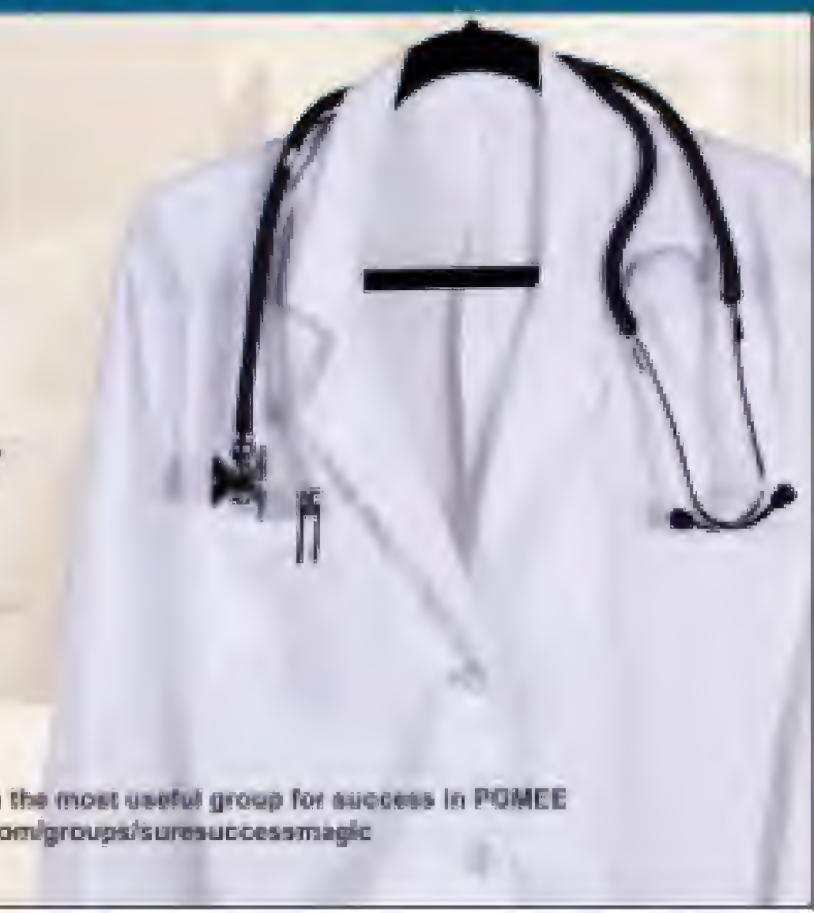
11th Edition

Sure Success MAGIC

Maximum Advantage Guide for Integrated Course Study

The Ultimate 'All-in-One' guide for PGMEE
For NEET-PG, AIIMS, PGI, JIPMER, DNBCET and FMGE

B Ramgopal



For exclusive book updates, join the most useful group for success in PGMEE
www.facebook.com/groups/suresuccessmagic

Contents

1. Embryology	1
2. Anatomy	16
3. Physiology	127
4. Biochemistry	182
5. Microbiology	226
6. Parasitology	276
7. AIDS	295
8. Immunology	306
9. Pharmacology	317
10. Pathology	372
11. Hematology	397
12. Genetics	423
13. Biostatistics	438
14. Preventive and Social Medicine	443
15. Forensic Medicine	490
16. Toxicology	525
17. Ophthalmology	535
18. Otolaryngology	605
19. Pediatrics	658
20. Orthopedics	708
21. Medicine	748
22. Surgery	869
23. Oncology	931
24. Obstetrics	963
25. Gynecology	997
26. Dermatology	1036
27. Venereology	1081
28. Psychiatry	1086
29. Anesthesiology	1122
30. Radiodiagnosis	1155
31. Radiotherapy	1190
32. Nuclear Medicine	1197
33. Hot Images!	1200
34. Most Recent Exams Roundup	1213

CHAPTER

1

Embryology

GROWTH FACTORS AND GENES IN EMBRYOGENESIS

Growth factors/ Genes	Functions
NODAL	<ul style="list-style-type: none"> Formation of primitive streak Formation of mesoderm
Lefty	<ul style="list-style-type: none"> Determination of body asymmetry
Sonic Hedgehog (SHH)	<ul style="list-style-type: none"> Neural tube formation Somite differentiation Organizes limbs in anteroposterior axis due to expression of SHH from the zone of polarizing activity (through vitamin A production) SHH mutations can lead to holoprosencephaly
WNT-7	<ul style="list-style-type: none"> Development of midbrain Organizes limbs in dorso-ventral axis
Homeobox (HOX)	<ul style="list-style-type: none"> Organizes structures in cranio-caudal direction Mis-expression of HOXB8 gene alters the position of the forelimbs during development
Bone morphogenic factors (BMP 1-9)	<ul style="list-style-type: none"> Bone formation Cell division and cell migration Apoptosis
PAX	<ul style="list-style-type: none"> PAX6-lens vesicle differentiation PAX2 over-expression causes failure of eyes to separate resulting in cyclops (single median eye)!
Fibroblast growth factors (FGF)	<ul style="list-style-type: none"> Mesoderm differentiation Angiogenesis Growth of axon Limb lengthening Development of brain Outgrowth of genital tubercle
Transforming Growth factor (TGF B1-B5)	<ul style="list-style-type: none"> Formation of extracellular matrix Epithelial branching Myoblast proliferation
Mullerian Inhibiting Factor	<ul style="list-style-type: none"> Regression of paramesonephric duct
Insulin-like Growth Factors (IGF)	<ul style="list-style-type: none"> IGF-1: Bone growth IGF-2: Fetal growth

SPERMATOGENESIS

- This refers to formation of spermatozoa (sperm) from primordial germ cells (**spermatogonia**)-it occurs in **seminiferous tubules** of the testes.
Spermatogonia undergo **Mitosis** to form **Primary spermatocytes (Diploid, 46 chromosomes, 4N)**
↓
These undergo **Meiosis** to form **Secondary spermatocytes (Haploid, 23 chromosomes, 2N)**
↓
These undergo **meiosis** to form **spermatids**
- Mnemonic: '**Mighty PleaseD Meiting Sec(x)y Happy girl!**'
- '**N Number**' has been explained below under 'Extra Edge'.
- In spermatogenesis **independent assortment** of paternal and maternal chromosomes occurs during **primary to secondary spermatocyte** stage.
- Time for **spermatogenesis = 74 days**.
- Spermatogenesis requires a **temperature lower than core temperature** (5°C lower); hence, **testes** are maintained at 32°C.
- The **number of spermatids** formed from a single spermatogonium is **512**.
- Spermatids do NOT divide further BUT undergo morphologic changes to form mature spermatozoa = **spermiogenesis** (i.e. it is last step of spermatogenesis)—takes place in the **Sertoli cells** of testis.
- Pathway of sperms:** Seminiferous tubules (**spermatogenesis** takes place here) → straight tubules (tubuli recti) → rete testis → efferent ductules → **epididymis** (here they **acquire motility**) → vas deferens → ejaculatory duct → prostatic urethra.
- Capacitation** means the physicochemical changes that occur in the sperm to make it capable of fertilizing the ovum.
- It occurs in the **fluid media of the female genital tract** and takes about **7 hours**.
- Only the capacitated sperms can penetrate the zona pellucida. Capacitated sperms move to **ampulla of Fallopian tube** where **fertilization** takes place.

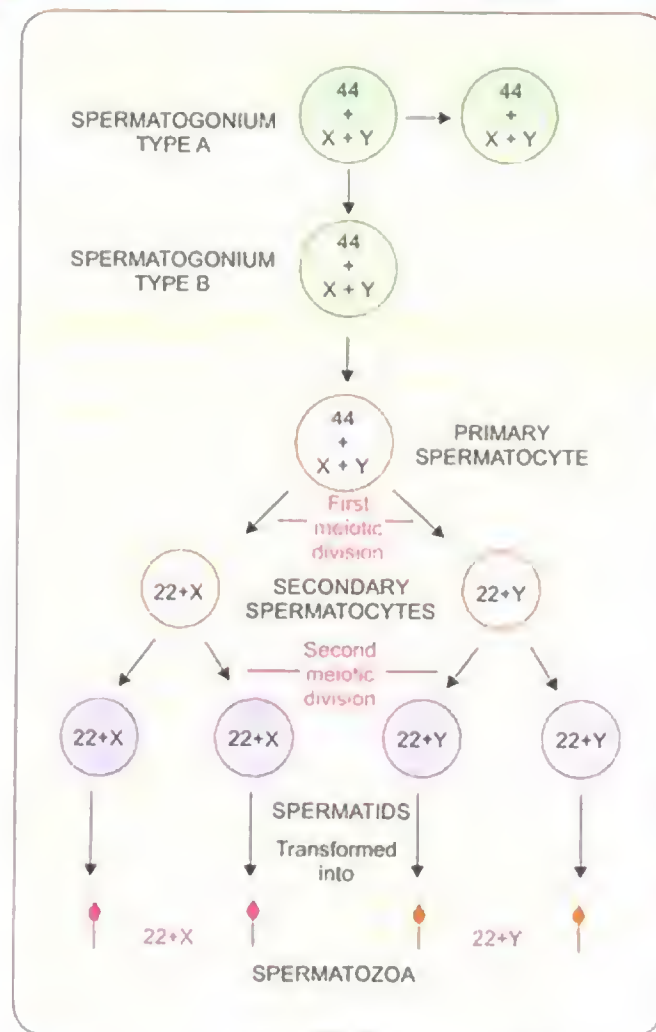


Fig. 1.1: Stages in spermatogenesis. Note the number of chromosomes at each stage

Spermatozoa (Sperm)

- Mature sperm is **55 to 65µ** in length.
- Sperm's Food = **Fructose**.
- **Sperms** move at about **3 mm/minute**.
- Fertilin-β, a protein of ADAM family present on sperm head, helps in sperm penetration through zona pellucida.
- Sperm parts:
 - **Head** (contains **acrosome** derived from **Golgi apparatus**)
 - **Neck** (has **centrioles**)
 - **Tail (flagellum)** has three parts: **Middle piece** derived from **Mitochondria**; **Principal piece** and **End piece**

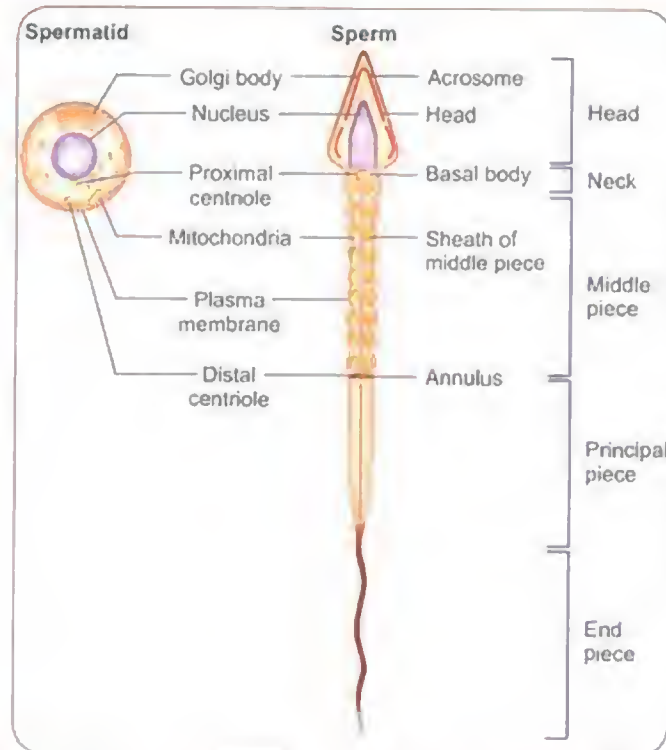


Fig. 1.2: Process of spermiogenesis in which different cell organelles of spermatid give rise to different parts of a sperm

Oogenesis

- **Oogenesis** refers to development of a mature ovum from primitive germ cells (oogonium)—it occurs in the ovaries.

Oogonia undergo **mitosis** to form **primary oocytes** (diploid, 46 XX) →

these primary oocytes enter a **prolonged prophase I** of first meiotic division - **prophase I** ('diplotene/dictyotene' stage) and remains in this stage until puberty

At **puberty just before ovulation**, the **first meiotic division** is completed and **secondary oocyte** (haploid, 23 chromosomes) and **1st polar body** are formed

Sec. oocyte immediately **begins second meiotic division** but this division **stops at metaphase** and is **completed only if the mature ovum (ootid)** is fertilized with the sperm. At that time **2nd polar body (polocyte)** is extruded and fertilized ovum proceeds to form a new individual.

- The secondary oocyte **completes the second meiotic division only after fertilization** by the sperm in the fallopian tube. **In the absence of fertilization, the secondary oocyte degenerates.**
- Remember! - **ovulation occurs** soon after formation of **secondary oocyte**.

Number	Remarks
7 million	Maximum number of primordial follicles at 20 weeks gestation
2 million	Total number of oocytes at birth
3-4 lakhs	Number of oocytes left behind at puberty , the rest being atretic.
400	Number of oocytes likely to ovulate during the entire reproductive period.
130µ	Diameter of fully mature ovum , the largest cell in the body (23, X).

- **Somatic cell** and **primordial germ cells** have two copies of each kind of chromosome and hence are **diploid**.
- In contrast, **mature gametes** (ovum and sperm) have just one copy of each kind of chromosome and are **haploid**.
- **N number** refers to the number of copies of each unique double stranded DNA molecule in the nucleus.
 - **Primary** spermatocyte/primary oocyte is **diploid, 4N**.
 - **Secondary** spermatocyte/secondary oocyte (including first polar body) is **haploid, 2N**.

Period of development after fertilization

1. **Pre-embryo** phase: 0-2 weeks
2. **Embryonic** phase: 3-8 weeks (most susceptible to **teratogens**)
3. **Fetal** phase: 9-38 weeks

PRE-EMBRYONIC PERIOD

Fertilization and Implantation (0-7 Days; 1st Week)

- **Fertilization** takes place in the **ampulla of Fallopian tube**.
- Fusion of sperm and ovum forms the **zygote**.
- **Zygote** cleaves by rapid **mitosis** into smaller daughter cells called **blastomeres** (still surrounded by zona pellucida) - occurs in the Fallopian tube.
- At **16 cell stage** blastomeres compact to form the **morula (mulberry)**.
- Morula **enters the uterine cavity** at **4 days after fertilization** and is converted into **blastocyst** in the uterine cavity.
- Blastocyst consists of:
 - **Outer Zona pellucida**
 - **Inner cell mass** called **Embryoblast**: forms **embryo proper**
 - **Outer layer of cells** called **trophoblast**: forms extraembryonic tissues.
 - **Blastocele**: Cavity of blastocyst.
- Zona pellucida is **shed off** from the blastocyst by **5th day** after fertilisation.
- At **6-7 days** after fertilization the **blastocyst attaches to endometrium** - implantation (bedding) - classically **interstitial implantation** in humans ('Blastocyst sticks on day six!').
- **Normal site of implantation**: posterior wall of the body of the uterus near the fundus.
- **Implantation** to uterine wall occurs in 3 stages—(i) **Apposition** (ii) **Adhesion** (iii) **Invasion**
- After implantation into the endometrium, the endometrium changes into **decidua**.

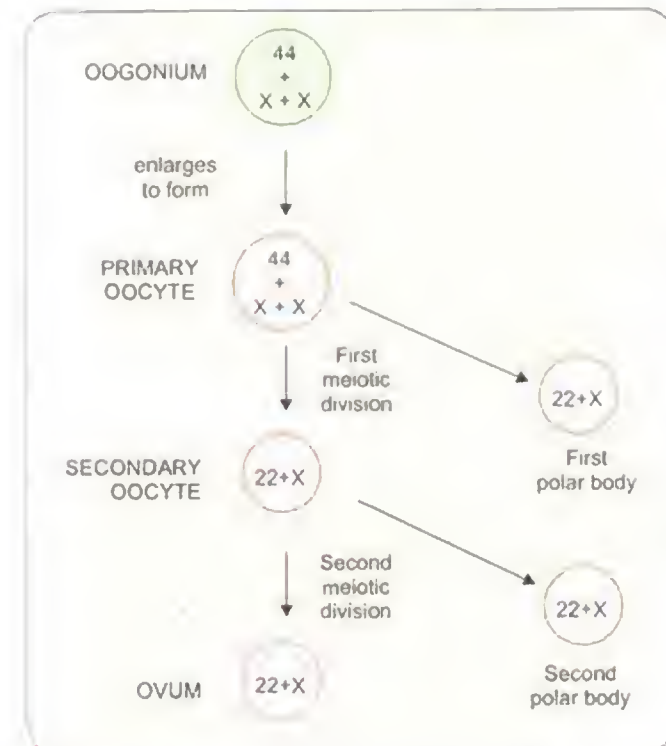


Fig. 1.3: Stages in oogenesis. Compare each stage with the corresponding one in Fig. 1.1

EXTRA EDGE

- Remember that **Primordial Germ Cells** (PGCs) originate in the **endoderm of the yolk sac**. Gametes (sperm and ovum) are derived from these PGCs which migrate into the developing gonads by the end of 5th week of development.
- **Ploidy** refers to the number of copies of each chromosome present in a cell.

EXTRA EDGE

- In **IVF** (In Vitro fertilization) **blastocyst** is implanted on **day 5** into the uterus.
- **HLA-G** is present on fetal trophoblastic tissue and helps in **maternal tolerance of the fetus** (i.e. it helps in preventing the maternal immune system from rejecting the fetus!).

2nd Week of Development

- Rule of 2s for 2nd week
 - **2 germ layers** (bilaminar germ disc): **epiblast** and **hypoblast**.
 - **2 cavities**: **amniotic cavity** and **yolk sac**.
 - **2 components to placenta**: **cytotrophoblast** and **syncytiotrophoblast**
- **Hypoblast** gives rise to **prochordal plate**: Indicates the future **site of mouth** and **establishes craniocaudal axis**
- **Extra embryonic mesoderm** is derived from the primary **yolk sac** (hypoblast).

EMBRYONIC PERIOD (3-8 WEEKS)

Embryonic Period is the stage during which, each of the three germ layers (ectoderm, endoderm and mesoderm) gives rise to its **own tissues and organ systems**.

Stage of Trilaminar Germ Disc—3rd Week

- **Gastrulation**: formation of **3 germ layers**—**ectoderm**, **mesoderm** and **endoderm**.
- Gastrulation begins with **formation of primitive streak** by proliferation of **epiblast cells** (ectoderm) near the **caudal end** of embryonic disc.
- Primitive streak is the **primary organiser** of the embryo and has at its cephalic end, the primitive node (**Hensen node**).
- **NODAL gene** initiates and maintains the integrity of the primitive node and primitive streak.
- Epiblast is the source of all 3 germ layers; **endoderm is the first germ layer to be formed**.
- Primitive streak regresses by **4th week (26th day)**.
- The **buccopharyngeal membrane** at the cranial end of the trilaminar germ disc consists of a small region of tightly adherent **ectoderm and endoderm** cells that represent the future opening of the oral cavity.
- **Notochord** is formed by **epiblast cells**; it defines the **axis** and provides central axis to the embryonic disc. It induces the overlying ectodermal cells to become neuroectodermal cells and form the neural tube.
- **Remnants of notochord** in adult: **nucleus pulposus** of intervertebral disc and **apical ligament of atlas vertebra**.

EXTRA EDGE

- Gastrulation is highly sensitive to teratogens during 3rd week (**caudal dysgenesis** - **sirenomelia** - **mermaid appearance** - fused lower limbs!).
- **Sacrocaecygeal teratoma** may arise from remnant of **primitive streak** (called **Hensen's node** or **primitive knot**).

Ectoderm

- A **Bone Morphogenic Protein (BMP)** regulatory network controls ectodermal cell fate decisions at the neural plate border
 - High BMP levels > epidermis formation
 - Low BMP levels > neural crest formation
 - BMP inhibition by **noggin**, **chordin**, **folliculin** > neural plate formation.

Neurulation

- **Neural tube** is formed from the closure of the **neural folds** which **begins** at the (future) **cervical region** (5th somite) and proceeds cranially and caudally.
- Until fusion is complete, the cranial and caudal end of the neural tubes communicate with the amniotic cavity by way of the cranial and caudal neuropores.
- Closure of **cranial neuropore** is complete by **day 25** and **caudal neuropore** by **day 27**.
- Neurulation is then complete and the CNS is represented by a closed tubular structure with a narrow caudal portion, the **spinal cord** and a much broader cephalic portion with dilations, the **brain vesicles**.

Mesoderm

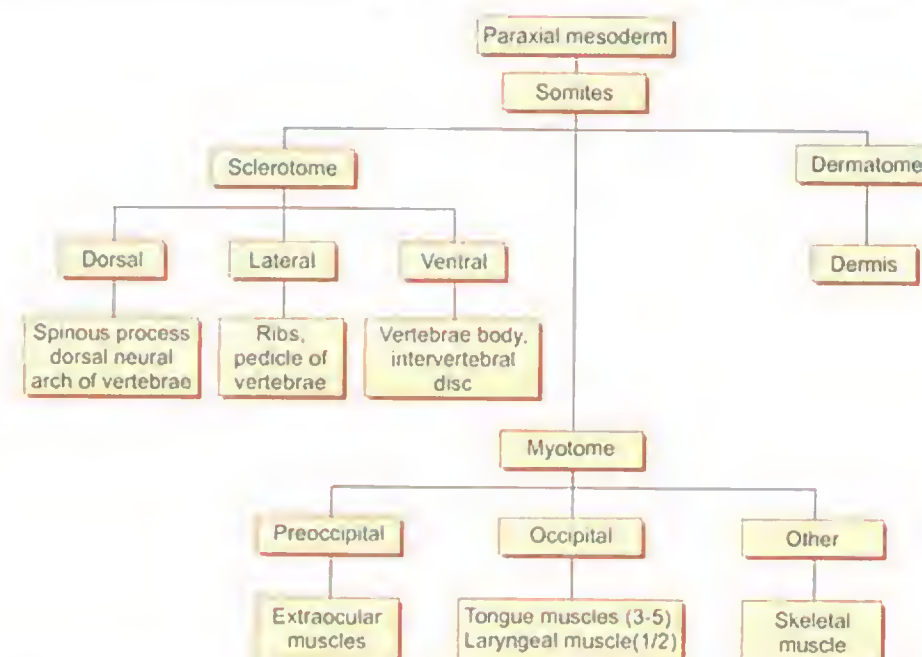
- Important components of the mesodermal germ layer are **paraxial**, **intermediate**, and **lateral plate mesoderm** (See flowchart on next page).

1. Paraxial mesoderm forms

- **Somitomes** in the region of the head—there are 7 of them and they form **bones and muscles of the head and jaw**.
- **Somites** in occipital and caudal segments.
 - The **earliest** cranial somites are formed in the **occipital region** and new somites are progressively formed caudal to them (**craniocaudal direction**).
 - Ultimately by the end of **5th week**, there are about **44 pairs** of somites (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 8-10 coccygeal).

- The **days 20-30** is called '**somite period of human development**'.
- Age of embryo upto 5 weeks is calculated by estimating the **number of somites** (forensic importance!).
- Each somite is divided into three parts - **medial sclerotome**; **middle myotome** and **lateral dermatome** (See Flowchart on next page).

- Intermediate Mesoderm**: Gives rise to **nephrotomes** and **nephrogenic cord** and ultimately forms the **genital ridge** and **urogenital system** (kidneys and gonads).
- Lateral Plate mesoderm**: Gives rise to **wall of the gut**, **pericardial**, **pleural** and **peritoneal cavities**. It also gives rise to smooth muscle component of **dorsal aorta/descending aorta**.



TIMELINE OF EVENTS AFTER FERTILIZATION

Age in days	Developmental events
1	Fertilization
2	Embryo two cell stage
3	Morula (16 cell stage) is formed
4	Morula enters uterine cavity; Early Blastocyst is formed
5	Late blastocyst formed
6-7	Implantation of blastocyst occurs
8	Bilaminar disc is formed; Trophoblast differentiates into cytotrophoblast and syncytiotrophoblast
9	Primary yolk sac forms
10-11	Embryo completely implanted into endometrium
12	Formation of extra-embryonic mesoderm
13	Formation of primary villi
14	Formation of prochordal plate and connecting stalk
15	Formation of primitive streak

Contd...

Contd...

Age in days	Developmental events
16	Intra-embryonic mesoderm is formed; disc is now three layered - gastrulation starts; Formation of secondary and tertiary villi
18	Formation of trilaminar embryonic disc
19	Neurulation begins; formation of neural plate
20	Formation of neural folds and neural groove
21	Formation of first pair of somites ; feto-placental circulation established
3-8 weeks	Internal organs develop
4th week	Forelimb buds appears (26th day) and hindlimb buds (28th day) Formation of face starts (continues upto 8th week) Heart begins to beat
8-12 weeks	Sex identifiable
10-12 weeks	Swallowing
11 weeks	Fetal breathing movements
12 weeks	Fetal urine formation occurs

GERM LAYER DERIVATIVES

	ECTODERM
Surface ectoderm	<ul style="list-style-type: none"> • Epithelial linings of lower anal canal; distal part of male urethra, external auditory meatus • Epidermis, hair, nails, sweat and sebaceous glands • External ear/Pinna • Inner ear (utricle, semicircular canals, vestibular ganglion of CN VIII, saccule, cochlear duct (organ of Corti), spiral ganglion of CN VIII, Olfactory placode) • Tooth enamel (ameloblasts), Lens of the eye • Corneal epithelium • Anterior pituitary, adenohypophysis (from Rathke's pouch—a thickened oral ectoderm), • Parotid gland • Mammary gland
Neuro-ectoderm	<ul style="list-style-type: none"> • Neural tube • All CNS neurons • Astrocytes, Oligodendrocytes, Ependymocytes, Tanycytes, choroid plexus cells • Neurohypophysis (posterior pituitary) • Pineal gland • Smooth muscles of iris (Sphincter and Dilator pupillae) • Optic vesicle and cup • Iris epithelium and Ciliary epithelium • Retina, Retinal pigment epithelium, Optic Nerve • Part of vitreous
Neural Crest	<ul style="list-style-type: none"> • Trunk Neural Crest cells • Melanocytes, Schwann Cells • Adrenal medulla (including chromaffin cells) • Dorsal root ganglia • Sympathetic chain ganglia; prevertebral sympathetic ganglia • Parasympathetic ganglia of the gut (Meissner's and Auerbach's plexus, CN X) • Abdominal/pelvic cavity parasympathetic ganglia • Cranial neural crest cells

Contd...

Contd...

ECTODERM
<ul style="list-style-type: none"> • Pia and arachnoid mater • Bones of cranium • Pharyngeal arch cartilage • Odontoblasts (dentin of teeth) • Parafollicular C cells of thyroid • Ciliary muscles • Corneal stroma and corneal endothelium • Aorticopulmonary septum, and endocardial cushions • Sensory ganglia of Cranial Nerves V, VII, IX and X (5,7,9,10) • Ciliary (CN III), Pterygopalatine (CN VII), submandibular (CN VII) and Otic (CN IX) parasympathetic ganglia.
MESODERM
<ul style="list-style-type: none"> • Epithelium of trigone of urinary bladder • Endothelium of blood and lymph vessels • Muscles (smooth, cardiac, skeletal), Connective tissue, Serous membranes, Bone and cartilage • Blood (RBCs, WBCs), lymph, Microglia and Kupffer cells • Organs - adrenal cortex, spleen, kidney, ureters, heart ACSCUH • Testes, epididymis, ductus deferens, seminal vesicles, ejaculatory duct • Ovary, uterus, uterine tubes, superior 1/3 of vagina • Extraocular muscles and ciliary muscles, sclera (temporal small portion), Iris, Choroid • Muscles of tongue (occipital somites/myotomes) • Arrector pili muscle of the skin (lifts hair to vertical position in cold environment) • Dura mater
ENDODERM

Epithelial lining of:

- GI tract
- Respiratory tract: pharynx, larynx, trachea, bronchi, lungs
- Urogenital tract: urinary bladder (except trigone), female urethra and most of male urethra, inferior 2/3 of vagina
- Tympanic cavity, middle ear, auditory tube, **pharyngotympanic tube** (Eustachian tube - from proximal part of tubotympanic recess)

Organs:

- **Liver (hepatocytes), gallbladder**, pancreas, thyroid, parathyroid, tonsils, glands of GI tract, lungs, submandibular and sublingual glands.

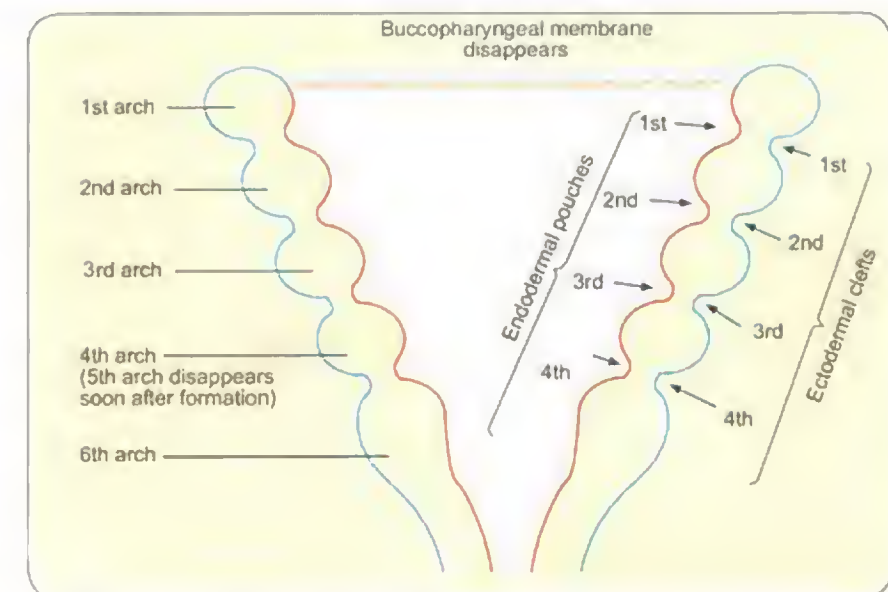


Fig. 1.4: Coronal sections through cranial part of foregut. Before, and after formation of pharyngeal arches

BRANCHIAL (PHARYNGEAL) APPARATUS

- Branchial apparatus is composed of branchial clefts, arches and pouches. ('CAP') from outside to inside.

- Branchial clefts – derived from *ectoderm*
- Branchial arches – derived from *mesoderm* and *neural crest*
- Branchial pouches – derived from *endoderm*.

Branchial Arch Derivatives

- Branchial arch 1** (Mandibular arch) 'The arch of *M*' ('Chewing and Listening' arch!)
- Muscles:** Muscles of Mastication (masseter, temporalis, medial and lateral pterygoids), Mylohyoid, Anterior belly of digastric, Tensor tympani, Tensor palati, anterior 2/3 of Tongue (**MMATTT**)
 - Cartilage (Meckel's cartilage):** Malleus and incus, sphenomandibular ligament.
 - Artery:** Maxillary A
 - Nerve:** Only arch having **double innervation**. *Chorda tympani* (branch of the facial N.) is the pretrematic N. while Mandibular N. (branch of trigeminal N, CN V) is the post-trematic N.
- Branchial arch 2** (Hyoid arch) 'The arch of *S*'
- Muscles:** Stapedius, Stylohyoid, posterior belly of digastric, Platysma, muscles of facial expression, auricular muscles, occipitofrontalis.
 - Cartilage (Reichert's)** forms (SS) - Stapes, Styloid process, Stylohyoid ligament, Smaller (lesser) cornu of hyoid, Superior part of body of hyoid.
 - Artery:** Stapedial artery
 - Nerve:** Facial nerve (CN VII)
- Branchial arch 3**
- Muscle:** Stylopharyngeus.
 - Cartilage:** Greater cornu of hyoid, Lower part of body of hyoid bone.
 - Nerve:** Glossopharyngeal N. (CN IX)
- Branchial arch 4** ('Swallowing' arch!)
- Muscles (4th arch):** most pharyngeal constrictors, *cricothyroid*, levator veli palatini
 - Cartilage:** Thyroid, cuneiform, epiglottis (from *hypobranchial eminence*), cricoid, arytenoids, corniculate
 - Nerve of 4th arch:** Superior laryngeal N. (branch of CN X)
- Branchial arch 6** ('Speaking' arch!)
- Muscles (6th arch):** All *intrinsic muscles of larynx except cricathyroid*
 - Nerve of 6th arch:** Recurrent laryngeal N. (branch of CN X)

EXTRA EDGE

- The 3rd, 4th and 6th arches do not have special names. The 5th arch disappears soon after formation so that only five arches remain.
- The above mentioned cranial nerves – V, VII, IX, X are the only ones with both motor and sensory components.
- The first (mandibular) arch develops two prominences – smaller maxillary prominence (forms maxilla, zygomatic bone, squamous temporal bone) and mandibular prominence (forms mandible).

Branchial Cleft Derivatives

- Dorsal part of 1st cleft = external auditory meatus.
- Ventral part of the 1st cleft obliterates
- 2nd through 4th clefts form temporary cervical sinuses and ultimately is obliterated; failure to obliterate leads to branchial cleft cyst.

Branchial Pouch Derivatives

Pouch	Derivative
1st pouch (ventral part)	Tongue

Contd..

Contd..

Pouch	Derivative
1st pouch (dorsal part)	Tubotympanic recess, which forms the eustachian tube and middle ear cavity Inner layer of tympanic membrane
2nd pouch (ventral part)	Tonsil
3rd pouch (Third pouch)	Thymus, Inferior parathyroid gland
4th pouch	Superior parathyroid gland Ultimobranchial body (Note: Neural crest cells migrate into the ultimobranchial body to form Parafollicular C-cells of thyroid)

EXTRA EDGE

- Aberrant development of 3rd and 4th pouches** → DiGeorge syndrome → leads to T cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development).
- First pharyngeal membrane** (which separates the 1st pharyngeal pouch from the 1st pharyngeal groove) forms the **tympanic membrane** and this represents **all three layers of the embryonic disc**
- Mnemonic:** You have 1 tongue and 2 tonsils—Thus tongue = 1st pouch and tonsil = 2nd pouch

GASTROINTESTINAL TRACT**Derivatives of the 'Gut'**

Fore-gut	Supplied by
<ul style="list-style-type: none"> Part of floor of mouth, including the tongue till the 2nd part of duodenum (upto major duodenal papilla) Liver, pancreas, biliary channels, spleen (mesoderm) Respiratory system 	Coeliac A.
Mid-gut	Supplied by
<ul style="list-style-type: none"> From descending (2nd part) of duodenum distal to major papilla till the right 2/3rds of transverse colon 	Superior mesenteric A.
Hind-gut	Supplied by
<ul style="list-style-type: none"> From left 1/3 of transverse colon till upper part of anal canal Parts of urogenital system derived from the primitive urogenital sinus 	Inferior mesenteric A.

Liver Development

- The **endodermal cells of the hepatic bud** give rise to the **parenchyma of the liver** and to bile capillaries.
- The **mesoderm of the septum transversum** forms the **capsule and fibrous tissue** of the liver.

Pancreas Development

- Pancreas forms from **ventral and dorsal buds (endoderm derived)** that rotate and fuse.
- Ventral bud** forms posterior/inferior head, uncinate process and main pancreatic duct.
- Dorsal bud** forms body, tail, anterior head. Acinar cells; Islet cells and accessory pancreatic duct.
- Annular pancreas** is a result of **failure of complete rotation of the ventral pancreatic bud**. It abnormally encircles the 2nd part of duodenum; forms a ring of pancreatic tissue that may cause **duodenal narrowing and non-bilious vomiting**.
- Pancreas divisum:** ventral and dorsal buds fail to fuse at 4 weeks.
- As pancreas develops at the junction of **foregut and midgut** its arterial supply is derived from **celiac artery (via superior pancreaticoduodenal artery)** as well as **superior mesenteric artery (via inferior pancreaticoduodenal artery)**.

CARDIOVASCULAR SYSTEM**Heart Tube Embryological Derivatives**

CVS is the first fully functional organ system in fetus and first to attain functional maturity

Embryonic structure	Gives rise to
Distal 1/3 of bulbus cordis (Truncus arteriosus)	Ascending aorta and pulmonary trunk
Middle 1/3 of bulbus cordis (Conus)	Forms outflow tract of right and left ventricles
Proximal 1/3 of bulbus cordis	Forms primitive right ventricle (Trabeculated part)
Primitive ventricle	Forms primitive left ventricle (Trabeculated part)
Primitive atria	Trabeculated left and right atrium
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium
Right common cardinal vein and right anterior cardinal vein	Superior vena cava
Left common cardinal vein	Oblique vein of left atrium
Right supracardinal vein, right subcardinal vein and right posterior cardinal vein	Inferior vena cava
Right supracardinal vein	Azygos vein
Left supracardinal vein	Hemiazygos vein

Aortic Arches and their Derivatives (Fig. 1.5)

- The **six pairs of aortic arches**, develop in a **cephalo-caudal direction** and interconnect the ventral aortic roots and the dorsal aorta.
- They are never all present in the developing human heart. Of the six pairs of aortic arches, **most of the 1st and 2nd arches disappear, 5th totally disappears**.

Aortic arch	Fate
1st arch	Mainly disappears, remaining part forms inferior alveolar artery (branch of maxillary artery)
2nd arch	Mainly disappears, remaining part forms stapedial artery
3rd aortic arch	Common carotid and proximal internal carotid artery
4th aortic arch (Right)	Proximal Right subclavian A. and brachiocephalic A.

Contd...

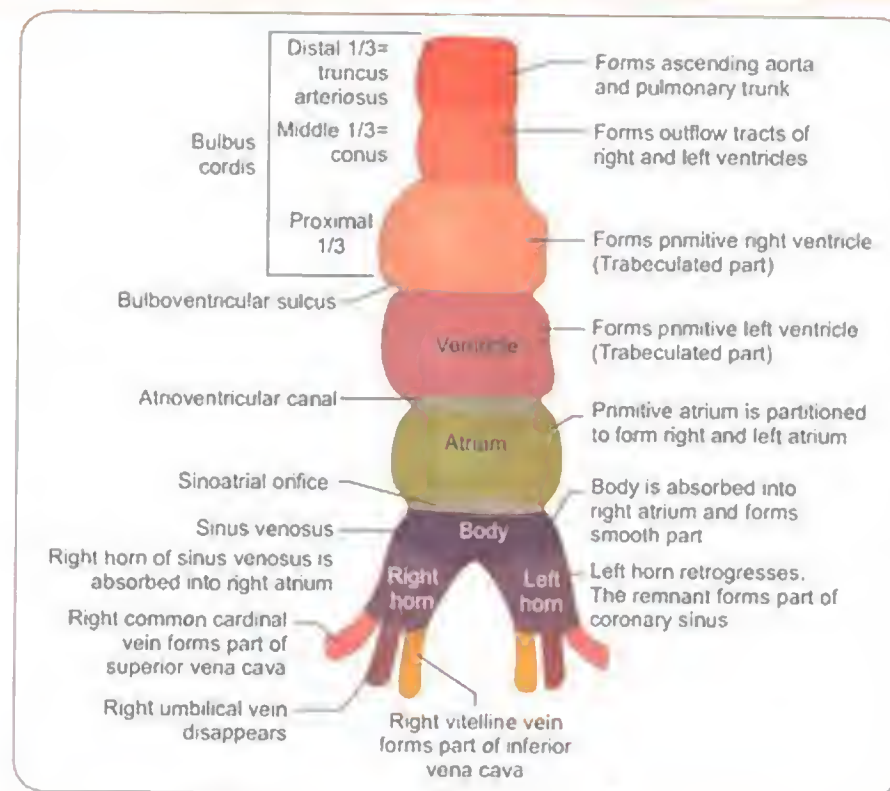


Fig. 1.5: Main subdivisions of the heart tube and their fate

Contd...

Aortic arch	Fate
4th aortic arch (Left)	Arch of aorta.
5th arch	DOES NOT develop in human embryo
6th aortic arch	Right and left pulmonary arteries and ductus arteriosus (on left only).

More Important Points about CVS Embryology

- **Left subclavian artery** is formed from the left 7th cervical intersegmental artery.
- The **portal vein** is formed by the right and left vitelline veins and anastomoses between them.
- The major **cardiac septa** are formed **between 5-7 weeks** of development.
- **Fossa ovalis** is the remnant of **septum primum**.
- **Foramen ovale** is the opening between the upper and lower limbs of the **septum secundum**.
- **Interatrial septum** is formed by the fusion of septum primum with septum secundum.
- **Double aortic arch** results when **right dorsal aorta** also persists distal to the origin of the **right 7th cervical intersegmental artery**.

Fetal-Postnatal Derivatives

Fetal structure	Post-natal derivative
Ductus arteriosus	Ligamentum arteriosum
Ductus venosus	Ligamentum venosum
Left umbilical vein	Ligamentum teres of Liver (contained in falciform ligament)
Right umbilical vein	Disappears
Vitello intestinal duct	Meckel's diverticulum
URachus (part of allantoic duct between bladder and umbilicus)	MediAN umbilical ligament
Obliterated umbilical ARtery	MediAL Umbilical fold
Lateral umbilical fold (epigastric fold)	Inferior epigastric artery
Proximal part of umbilical Artery	Superior vesical A.
Distal part of umbilical Artery	Lateral umbilical ligament

EXTRA EDGE

- Mnemonic: '**ANURiA** is **ALARming!!**' (Medi**AN** umbilical ligament- **UR**achus; Medi**AL** umbilical fold - obliterated umbilical **AR**tery).
- A **patent urachus** may form a **urachal fistula** between the umbilicus and dome of the urinary bladder; may present with **watery discharge from umbilicus** (urine stained) on straining; treat by **surgical excision**; **adeno Ca** or **TB** may occur in patent urachus.

URINARY SYSTEM

Kidney Embryology

- **Pronephros**—until week 4, then **degenerates**.
- **Mesonephros**:
 - Functions as **interim kidney for 1st trimester** and then **regresses**; in males the **mesonephric (Wolffian) ducts persist** which later contributes to **male genital system**.
 - Gives rise to **ureteric bud** which gives rise to **collecting part of the kidney (pelvis of kidney, major, minor calyces, collecting tubules)** - fully canalised by 10th week.
 - Gives rise to ureteric diverticula which form the ureters
- **Metanephros**—forms the **definitive adult kidney**, gives rise to **renal parenchyma** (nephrons - PCT, DCT, Henle's loop, **glomerulus**)
- **Urogenital sinus**—develops into **bladder, urethra** and **allantois**
- Between weeks 5 to 8 of embryonic development, each kidney ascends the posterior abdominal wall to reach its normal position in the loin. At the same time it **rotates, 90 degrees** so that its hilum faces medially **instead of ventrally** as it did previously
- Nonunion of secretory and collecting part of kidney results in **congenital polycystic kidney**.

Urinary Bladder Embryology

- The urinary bladder is formed from the upper portion of the **urogenital sinus** which is continuous with the allantois.
- The **epithelium of the urinary bladder** develops from the **cranial part of the vesicourethral canal (endoderm)**.
- The **epithelium of trigone** of the bladder is derived from the **absorbed mesonephric ducts (mesoderm)**.
- The muscular and serous coats are derived from splanchnopleuric intraembryonic mesoderm.

Development of Urethra

Remember that the female urethra and MOST of the male urethra are derived from **endoderm** except the **Posterior wall of prostatic urethra** that is derived from the absorbed mesonephric ducts (**mesoderm**).

Urethra	Embryonic source
Female Urethra	Caudal part of vesicourethral canal. Pelvic part of definitive urogenital sinus.
Male urethra	
Prostatic Urethra	
1. Above openings of ejaculatory ducts (colliculus seminalis)	Caudal part of vesicourethral canal.
2. Below openings of ejaculatory ducts	Upper pelvic part of definitive urogenital sinus.
Membranous urethra	Lower pelvic part of definitive urogenital sinus.
Penile urethra	Phallic part of definitive urogenital sinus.
Terminal part of penile urethra (within glans)	Surface Ectoderm

GENITAL HOMOLOGUES IN MALE AND FEMALEA

Male	Undifferentiated	Female
Glans penis	← Genital tubercle →	Glans clitoris
Corpus spongiosum		Vestibular bulbs
Bulbourethral glands of Cowper	← Urogenital sinus →	Bartholin's greater vestibular glands
Prostate gland		Urethral and paraurethral glands of Skene
Ventral shaft of penis (penile urethra)	← Urogenital folds →	Labia minora
Scrotum	← Labioscrotal swelling →	Labia majora
Gubernaculum testis	← Gubernaculum →	Ovarian and round ligaments

Contd...

Contd...

Male	Undifferentiated	Female
(SEED) Seminal vesicles Epididymis Ejaculatory duct Ductus (Vas) deferens Paradidymis (<i>mesonephric tubules</i>)	← Mesonephric (Wolffian) duct →	Gartner's duct Epoophoron, Paroophoron
Appendix of testis Prostatic utricle	← Paramesonephric (Mullerian) duct →	Fallopian tube Uterus and Upper part of vagina

EXTRA EDGE

- Mnemonic: **M**esonephric (**W**olffian) duct - gives rise to male genital parts - '**M**ales are **W**olves'; Similarly, **P**aramesonephric (**M**ullerian) duct gives rise to female genital parts - '**P**(f)e**M**ales'
- In addition, the **mesonephric duct in males** also gives rise to
 - Ureteric buds,
 - Trigone of urinary bladder;
 - Posterior wall of prostatic urethra cranial to openings of ejaculatory ducts and
 - Appendix of epididymis.
- The **ovaries** begin to become **distinguishable from the testis** by **8 weeks** of gestation.

DESCENT OF TESTIS

- At first the testes lie on the dorsum of the abdominal wall. During foetal life they gradually descend to the scrotum.
- Gubernaculum testis** is a mesenchymal cord that extends from the caudal pole of the testis to the inguinal canal—plays a crucial role in descent of the testis—at the end of descent it is reduced to the scrotal ligament that connects the lower pole of the testis to the scrotal wall.

Testes reach the **Iliac fossa** during the **3rd month**



Lie at the site of the **deep inguinal ring** up to **7th month**.



They pass through the inguinal canal during the **7th month** and



are at the **superficial inguinal ring** by the **8th month**.



Testes enter the **scrotum** in the **9th month**.

Cryptorchidism

- MC on right side and bilateral in 20%** cases.
- It may be Intra-abdominal anywhere along its path of descent OR ectopic (MC, ectopic site is within superficial inguinal pouch).
- Complications:
 - Infertility** (MC complication)—as puberty approaches, the cryptorchid testis atrophies.
 - Hernia: Incompletely descended testes (cryptorchidism)** is a/w **patent processus vaginalis in 90% of cases**, although incidence of hernia is much lower.
 - Malignancy: 5-10 times** greater risk; MC malignancy in cryptorchid testis is **seminoma**
 - Testicular Torsion**
- Orchidopexy** is usually performed **before 12 months** of age.

CNS EMBRYOLOGY**Parts of Developing Brain and their Adult Derivatives**

Nervous system develops from the **neuroectoderm**. CNS develops from the neural tube that shows three dilatations, craniocaudally as given in the following table.

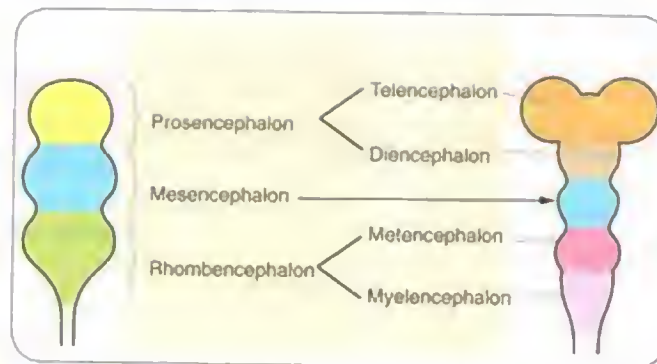


Fig. 1.6: Primary brain vesicles and their subdivisions

Neural tube vesicle	Embryologic subdivision of brain	Adult derivatives	Cavity
Prosencephalon (Fore-brain)	Telencephalon	Cerebral cortex Basal ganglia Olfactory bulbs Limbic system Corpus striatum Corpus callosum Hippocampus Amygdala	Lateral ventricles (right and left)
	Diencephalon	Thalamus, hypothalamus, epithalamus, metathalamus, subthalamus, optic stalk, retina, posterior pituitary	3rd ventricle
Mesencephalon		Midbrain	Cerebral aqueduct
Rhombencephalon (Hind-brain)	Metencephalon	Pons and cerebellum Middle cerebellar peduncles	Fourth ventricle
	Myelencephalon	Medulla oblongata Inferior cerebellar peduncles	

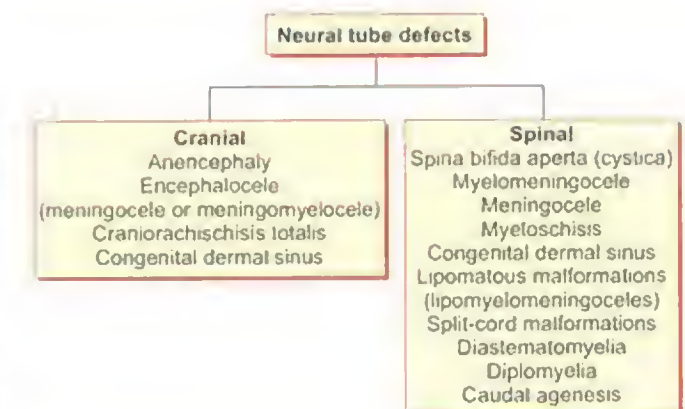
Important CNS MCQ Points

- The developing **neural tube** is divided into
 - 'Alar' lamina: **Dorsal; sensory** or afferent
 - 'Basal' lamina: **Ventral; motor** or efferent
- Similarly, in the spinal cord, the **alar lamina** forms the **posterior horn** and the **basal lamina** forms the **anterior (ventral) horn**.
- Derivatives from **alar lamina**:
 - Cerebellum,
 - Colliculi,
 - Substantia nigra.
- Nuclei from Basal lamina**: Nuclei of CN III, IV, VI, XII; motor nucleus of CN V, VII; dorsal nucleus of CN X (vagus); superior and inferior salivatory nucleus, lacrimal nucleus, Edinger-Westphal nucleus and nucleus ambiguus.
- Neuronal migration** is complete by 6th month (3-5 months is the peak period of neuronal migration).

Neural Tube Defects

- Open NTDs** frequently involve the **entire CNS** (e.g. associated hydrocephalus, Chiari II malformation) and are due to **failure of primary neurulation**. Neural tissue is exposed with associated cerebrospinal fluid (CSF) leakage
- Closed NTDs** are localized and **confined to the spine** (brain rarely affected) and result from a **defect in secondary neurulation**. Neural tissue is not exposed and the defect is fully epithelialized, although the skin covering the defect may be dysplastic.

- NTDs may have cranial or spinal presentation:

**Anencephaly**

- Failure of **anterior neuropore** to close; no brain/calvarium, a/w **polyhydramnios**; incompatible with extrauterine life.
- Also know: **Iniencephaly** is a condition where the neonate's head is bent severely backward and spine is distorted; child does not live longer than few hours.
- Note:** **Anterior neuropore** closes by **day 25** and **posterior neuropore** by **day 27**.

Spina Bifida

- MC type** of NTD; **Lumbosacral region MC** affected; **posterior neuropore** fails to close; bony vertebral arches fail to close

- **Spina bifida Occulta:** MC type of spina bifida; mildest form, evidenced by tuft of hair; skin is intact, NO disability.
- **Spina bifida cystica:** Cystic swelling on back is seen. 3 types are:
 1. **Meningocele:** Meninges protrude through vertebral defect; a sac of fluid that protrudes through an opening in the back but spinal cord not involved
 2. **Myelomeningocele:** Second MC type of spina bifida and more severe form of spina bifida; spinal cord tissue forms a part of the sac.
 3. **Rachischisis:** Most severe; spine lies wide open and often a/w anencephaly; paralysis from the level of defect downward.

Detection and Prevention of NTDs

NTDs are detected by **elevated maternal serum AFP** and prenatal U/S; can be prevented by use of **folic acid** during pregnancy.

Brain Development Anomalies

- Holo-prosencephaly** a/w mutation in *sonic hedgehog* gene; Decreased separation of hemispheres across midline; results in cyclopia; a/w **Patau's syn.** and severe fetal alcohol syndrome.
- Porencephaly** **Cyst or cavity** in the cerebral hemisphere lined by white matter; can be detected by skull transillumination in infancy.
- Lissencephaly** = **smooth** brain, absence of sulci and gyri in the brain.
- Schizencephaly** **Slits or cleft** in cerebral hemisphere lined by heterotopic grey matter



Fig. 1.7: Spina bifida occulta: Lumbosacral hypertrichosis



Fig. 1.8: Occipital encephalocele: newborn infant with massive occipital encephalocele. It is a neural tube defect that involves extrusion of cranial contents through a bony defect



Fig. 1.9: Myelomeningocele: symptoms vary depending on the level of the lesion: Thoracic myelomeningocele

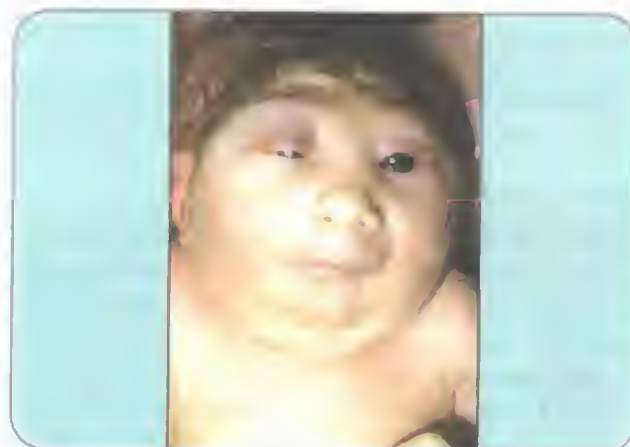


Fig. 1.10: Anencephaly: The lack of normal development of the brain, skull and scalp. Diagnosed prenatally by maternal AFP screening and foetal ultrasonography

TONGUE DEVELOPMENT

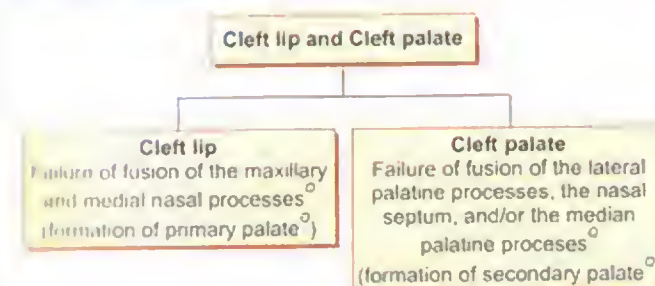
Anterior 2/3	Posterior 1/3	Posteriormost part
From lingual swellings from 1st branchial arch	From cranial end of hypobranchial eminence (cupola of His) of 3rd branchial arch	From 4th branchial arch
Taste by Chorda Tympani (branch of CN VII); General sensation by Lingual N (branch of CN V) mandibular N	Both taste/general sensation by CN IX.	Both taste/general sensation by CN X. (internal laryngeal N-a branch of superior laryngeal N-a branch of vagus)

EXTRA EDGE

- Overall for tongue, **Taste:** CN VII, IX, X (**solitary nucleus**)
- Overall for tongue, **General sensation, pain:** CN V3, IX, X
- Overall for tongue, **Motor:** CN XII
- **Tongue** muscles are derived from **occipital myotomes**.

MORE IMPORTANT EMBRYOLOGY TOPICS

Cleft Lip and Palate



Embryology of Diaphragm

- Diaphragm is formed by the fusion of
 - Dorsal esophageal mesentery,

- Septum transversum (forms **central tendon**)
- Pleuroperitoneal membranes
- Body wall mesoderm
- **Mnemonic:** 'Diaphragm Separates Pleura from Below'
- Diaphragm innervation - **C3, C4, C5 (Phrenic. N.)** 'C3, 4, 5 keeps the diaphragm alive!' - ALSO remember that diaphragm develops from **cervical somites 3, 4, 5**.

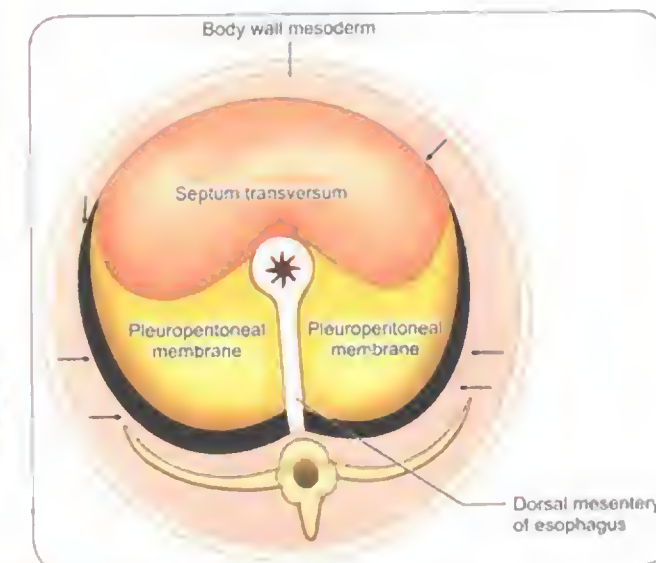


Fig. 1.11: Developmental sources of diaphragm (arrows indicate contribution of body wall mesoderm). The muscle of the diaphragm develops from cervical myotomes; hence the nerve supply by phrenic nerve

Thyroid Gland Development

- Develops from **thyroglossal diverticulum**, which pushes out from the tongue at the foramen caecum.
- MC site of **ectopic thyroid** = **tongue**.

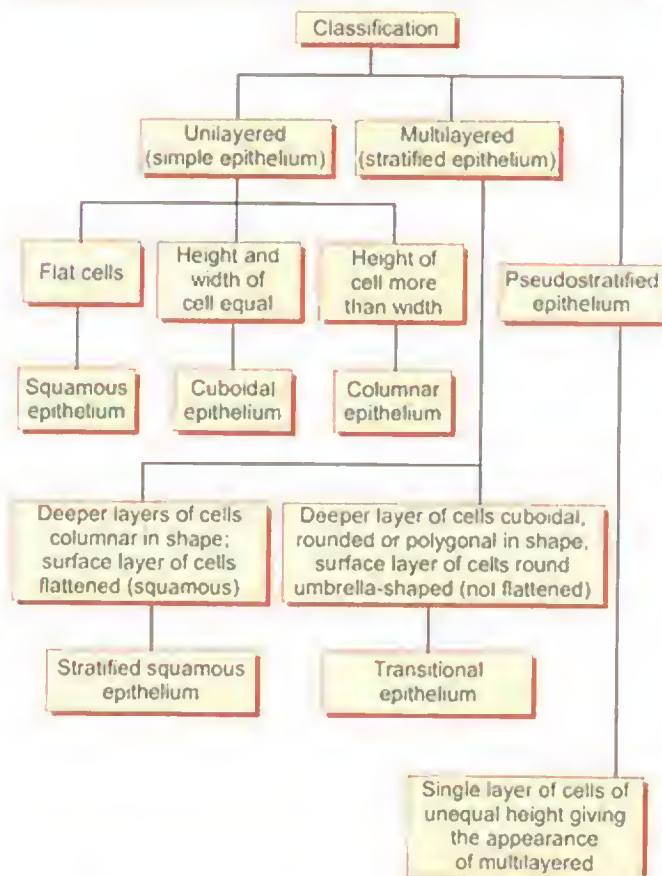
Omphalocele Vs Gastroschisis

	Omphalocele	Gastroschisis
Location	Within umbilical cord	Peri-umbilical (usually to right of cord)
Covering	Membranous sac	None (exposed viscera)
A/w prematurity	30%	60%
Surgical intervention	Not urgent	Urgent
Prognostic factors	Associated anomalies	Condition of the bowel
Associated conditions	More common <ul style="list-style-type: none"> • Congenital Heart Disease • Beckwith-Wiedemann syndrome • Trisomy 13, 18, 21 • Pentalogy of Cantrell • Exstrophy of bladder • Malrotation of GUT 	Rare <ul style="list-style-type: none"> • Intestinal atresia • Malrotation of GUT

GENERAL ANATOMY

EPITHELIUM

Flowchart 2.1: Classification of epithelia



- **Simple squamous (pavement) epithelium:**
 - **Endothelium** of blood vessels and heart (**endocardium**)
 - **Mesothelium** of serous membranes (**pleura, pericardium and peritoneum**)
 - Epithelium of **lung alveoli**
 - Epithelium of **loop of Henle (Ansa nephroni)** and parietal layer of **Bowman's capsule**.

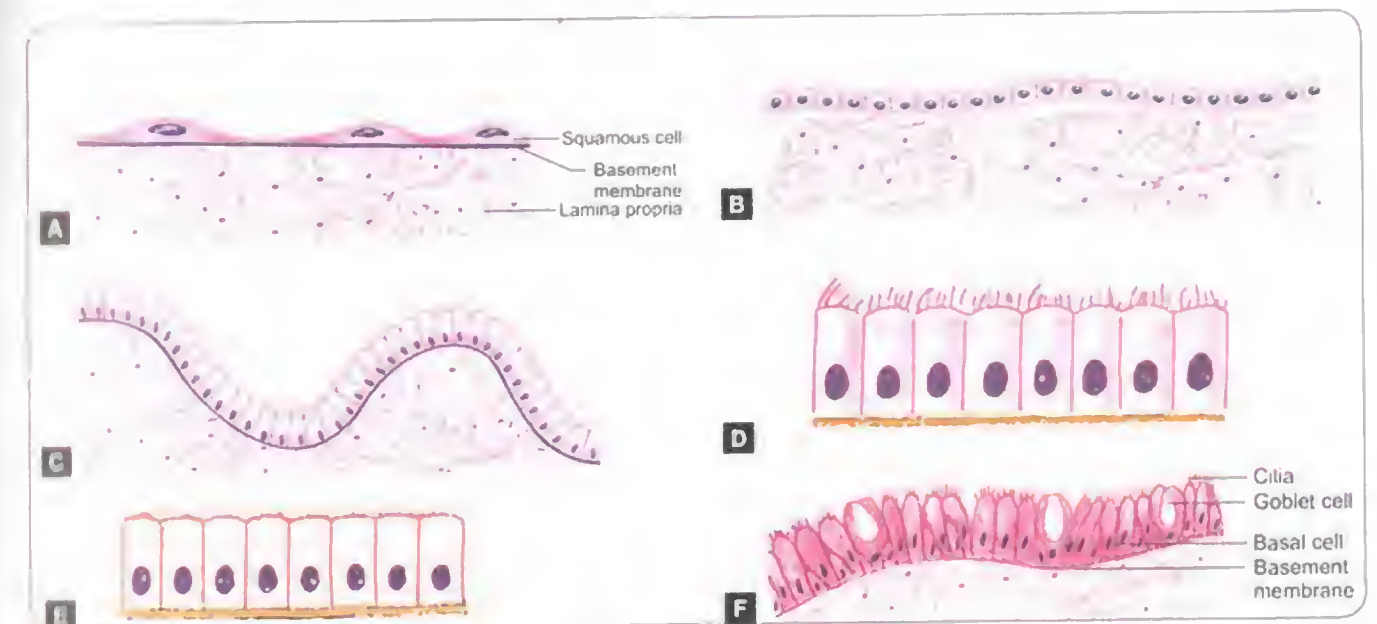
- **Simple cuboidal epithelium:** Seen in
 - Epithelium of **proximal and distal convoluted tubules** of kidney (**with brush border**)
 - **Retinal pigment epithelium**, inner surface of the **lens**.
 - Surface of the **ovary**
 - Follicles of **thyroid gland**
 - **Choroid plexus**
- **Simple columnar epithelium (without cilia and microvilli):** Seen in
 - Lining of **stomach** and **large intestine**
 - **Cervical canal**.
- **Simple columnar epithelium with brush border (irregularly placed microvilli):** Seen in lining of **gall bladder**
- **Simple columnar epithelium with striated border (regularly placed microvilli):** Seen in **Small intestine**
- **Ciliated columnar epithelium (Simple columnar epithelium with cilia):** Seen in
 - **Gallbladder tube**,
 - **Uterus**,
 - Efferent ductules of the **testis**,
 - **Eustachian tube**,
 - **Tympanic cavity**
 - **Central canal of spinal cord**.
- **Pseudostratified Epithelium:** NOT a true stratified epithelium BUT appears to be stratified since the nuclei of the columnar epithelium appears to be arranged in two or more layers. All the cells are attached to the basement membrane and some are short and basal while others are tall and columnar.
 - **Nonciliated pseudostratified columnar epithelium:** seen in some parts of Eustachian tube; the ductus deferens and male urethra (membranous and penile parts).
 - **Ciliated pseudostratified columnar epithelium:** seen in **trachea** and large bronchi

- **Pseudostratified columnar epithelium with stereocilia** (long microvilli): seen in **epididymis**.
- **Stratified squamous keratinised epithelium:**
 - Epidermis of **skin** of whole body
 - **Vestibule** of nose
 - External auditory meatus
 - Ducts of **sebaceous glands**
- **Stratified squamous non-keratinised epithelium:** Seen in epithelium of:
 - **Cornea** and **conjunctiva**
 - Oral cavity, **tongue**, **esophagus**, **pharynx** and part of **anal canal**.

- **Vagina**
- **Stratified columnar and cuboidal epithelium:**
 - **Large ducts of sweat glands, salivary glands and pancreas.**

Transitional epithelium

- Seen mainly in **urinary tract**—hence **urothelium**.
- these cells have **extra reserve of cell membrane**.
- It consists of cuboidal cells in basal layer, polygonal cells in middle layer and large umbrella cells in top layer (which are exposed to urine).
- Found in: **renal pelvis, calyces, ureter, urinary bladder and proximal portion of urethra**.



Figs 2.1A to F: Microscopic structure of (A) Squamous epithelium; (B) Cuboidal epithelium; (C) Simple columnar epithelium; (D) Columnar epithelium showing cilia; (E) Columnar epithelium showing a striated border made up of microvilli; (F) Pseudostratified ciliated columnar epithelium

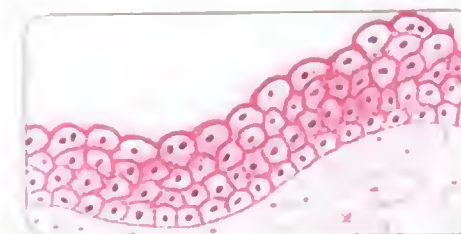


Fig. 2.2: Microscopic structure of transitional epithelium

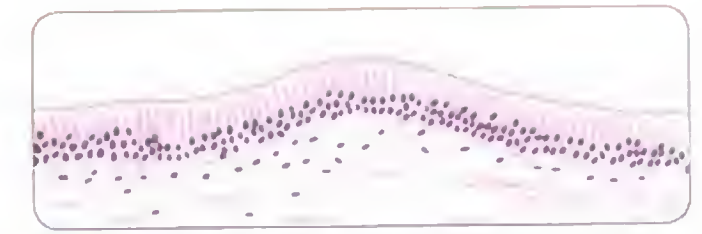
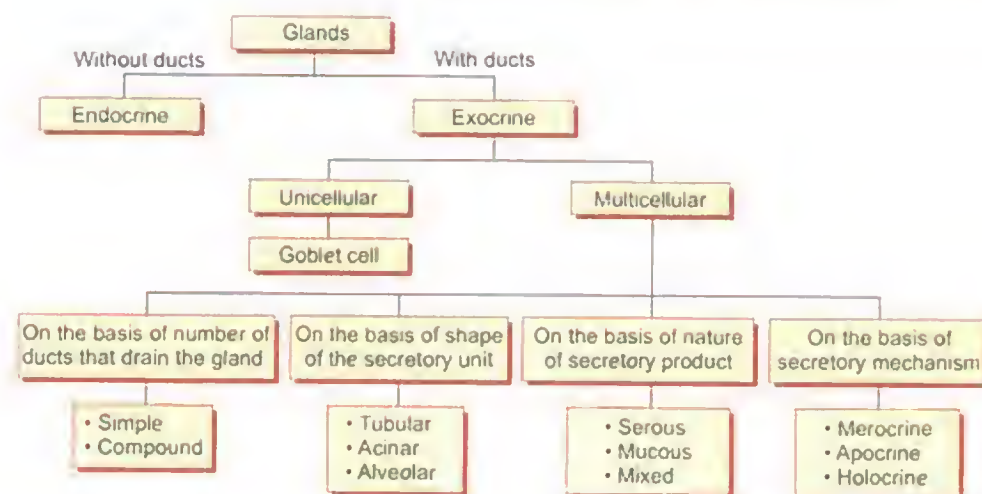


Fig. 2.3: Pseudostratified columnar epithelium as seen in a section

GLANDS

Flowchart 2.2: Classification of glands



Glands—Depending on Mode of Secretion

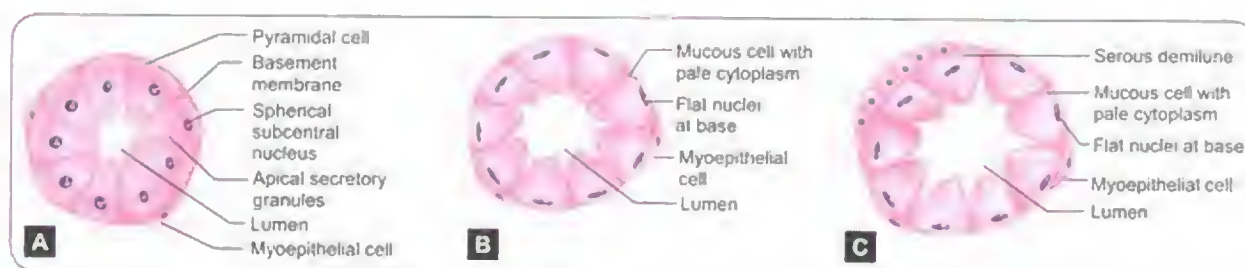
- **Apocrine glands**—Apical part of cell is shed off to discharge secretion (*decapitation* secretion). Responds mainly to sympathetic adrenergic stimuli; becomes functional at puberty. Examples are:
 - sweat glands in *axilla* and *groin*
 - *mammary* glands
 - *external auditory canal* (ceruminous gland)
 - *eyelids* (gland of *Moll*)
- **Holocrine glands**—Entire (*whole*) cell disintegrates discharging secretion. Ex: *sebaceous* glands. Found throughout skin *except palms and soles*. *Sebaceous glands* are usually a/w hair follicles except in following locations
 - Gland of *Zeis* and *Meibomian* gland: in eyelids
 - *Montgomery* tubercle: nipple and areola
 - *Tyson's* gland: external fold of prepuce (genitalia)

➤ **Fordyce spot**: vermillion border of lips and mucosa

- **Eccrine glands** (Merocrine)—Cell is intact, secretions are thrown out by exocytosis. (*Eccocytosis*). Eccrine gland has 3 portions: *acrosyrngium*, *straight duct* (has eosinophilic cuticle) and *secretory coil*. Eccrine glands are found *everywhere except* clitoris, gland penis, labia minora, external auditory canal and lips. Examples are:
 - Sweat gland on palms, soles and goblet cells.

Glands—Depending on Type of Secretion

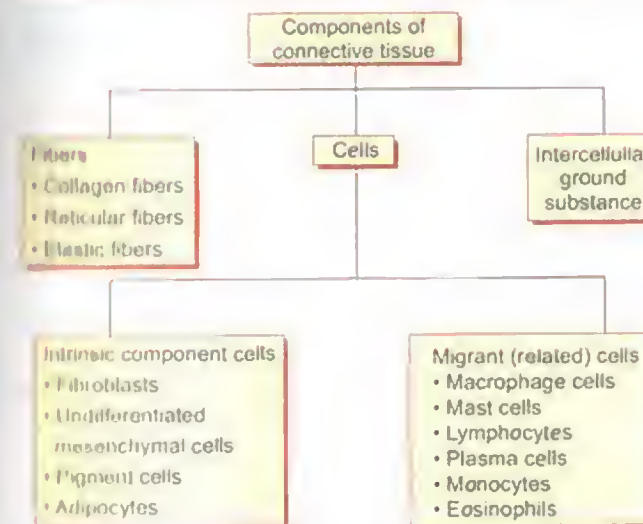
- **Serous**: Watery fluid containing protein (ex: *parotid* and lacrimal glands)
- **Mucous**: Viscous secretion containing mucus (Ex: esophageal glands; pyloric glands; *sublingual* salivary glands)
- **Mixed**: Ex: *Submandibular* salivary glands (has *serous demilunes*)



Figs. 2.4A to C: Types of acini (A) Serous; (B) Mucous; (C) Mixed

CONNECTIVE TISSUE

Flowchart 2.3: Basic components of connective tissue



Loose (Areolar) Connective Tissue

- **Most abundant** in the human body as it forms the stroma of organs and tunica adventitia of blood vessels.
- Abundant ground substance is present BUT poor in fibers and connective tissue cells.
- **Fibroblasts** is the MC cell type

Dense Connective Tissue

- Contains thicker and densely packed collagen fibrils predominantly with less ground substance and cell types (hence also called white fibrous tissue).

Dense irregular connective tissue

Arranged in sheets or layers with fibers randomly interwoven
Found in:

- Reticular layer of *dermis*
- *Periosteum*
- *Perichondrium*
- *Submucosa* of alimentary canal
- Forms *capsule* of lymph nodes, spleen, testes and liver;
- *Sclera*

Dense regular connective tissue

Arranged in cords/bands with fibres arranged parallel, evenly spaced and tightly packed.
Found in:

- *Tendons*,
- *Ligaments*,
- *Aponeuroses*;
- *Pericardium*,
- *Dura mater*;
- *intermuscular septa* and
- *Corneal stroma*

Collagen Fibres

- Collagen is the **most abundant protein** in the human body—highest in skin (74%) and next in cornea (64%)

- Collagen has a **triple helix structure** consisting of three amino acids: **mainly glycine** (which constitutes every third residue, almost 35%), **proline** and **hydroxyproline** (together 25%).
- The three strands are **hydrogen bonded** to each other.
- **Hydroxyproline** is important in **stabilizing** the triple helical structure of collagen.
- The hydroxylation of proline and lysine requires molecular oxygen and a reducing agent such as **Vitamin C (ascorbic acid)**.
- **Alpha chain**—**Polyproline helix** of three residues per turn is twisted in **left handed** direction. Three of these alpha chains are then wound into a **right handed superhelix**.
- Each triple helical unit is displaced longitudinally from its neighbour by slightly less than one-quarter of its length—"**quarter staggered arrangement**".

Types of Collagen

Type	Tissue distribution
I (MC type, 90%; large diameter-250 nm)	Skin, bone, tendon, ligament, cornea, dentin, fascia, meninges, late wound repair (Type <u>one</u> = <u>bone</u> , tendon, <u>cornea</u>)
II	Cartilage (including hyaline), nucleus pulposus, notochord, vitreous body (Type <u>two</u> = <u>Cartilage</u>)
III	Fetal skin, uterus, blood vessels ; " reticular fibres ", granulation tissue, uterus; vascular type of Ehlers Danlos syndrome (type three E-D , 3D)
IV	Basement membrane , (type IV-under the floor!) Descemet's membrane, kidney glomeruli, lens capsule

EXTRA EDGE

- **Clue**: In the above table as the "number" of the type of collagen increases, the strength decreases!
- More than **25 types** of collagen are recognized.
- Major collagen in **hypertrophic cartilage**: type X.
- Major collagen in skin **hemidesmosomes**: type XVII (17)
- Major collagen in **rhabdomyosarcoma** cells—type XIX (19).
- **FACIT collagen** = "**Fibril Associated Collagen with Interrupted Triple helix**". The prototype of FACIT collagen is Collagen IX. (Other FACIT collagens include collagens 12, 14, 16, 21)

Ehlers-Danlos Syndrome (EDS)

- Due to defective collagen
- Characterized by hyperelastic skin (rubber person syndrome) and hypermobile joints.
- MC collagen affected is type III collagen

Villefranche Classification of EDS

Subtype	Defect in	Comments
Classical	Type I and V collagen	Classic clinical features
Hypermobile (type III EDS-MC type)	Type III collagen; tenascin X	Joint hypermobility is most prominent
Vascular (type IV EDS)	Type III collagen	Most serious type; sudden death may occur due to rupture of large blood vessels or hollow organs
Kyphoscoliotic (type VI EDS)	Lysyl hydroxylase	Mutations in PLOD1 gene
Arthrochalasia (type VIIA, B)	Type 1 procollagen	
Dermatosparaxis (type VIIC)	ADAM metalloproteinase with thrombospondin type 1 motif (procollagen N proteinase)	

Elastic Fibres

- Elastic fibres are mainly composed of Elastin-present within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava.
- Rich in nonpolar amino acids—glycine, alanine, valine, and proline residues.
- Tropoelastin is with fibrillin scaffolding.
- Elastin is broken down by elastase which is normally inhibited by alpha-1-antitrypsin.
- Mutations in elastin gene leads to supravalvular aortic stenosis (**Williams-Beuren syndrome**) and **cutis laxa**.
- Marfan syndrome is caused by defect in fibrillin, a glycoprotein that forms a sheath around elastin.
- Emphysema** can be caused by alpha-1-antitrypsin deficiency resulting in excess elastase activity.

Reticular Fibres

- They are **synthesised by fibroblasts** and reticular cells (special variety of fibroblasts).
- Mainly composed of **type III collagen**; they are stained by silver impregnation which renders them black (type I collagen stains brown with silver)—hence called **argyrophilic fibres**.
- Reticular fibres provide a supporting network in lymphoid organs like **spleen, lymph nodes and bone marrow**; most glands, including the **liver and kidneys**.

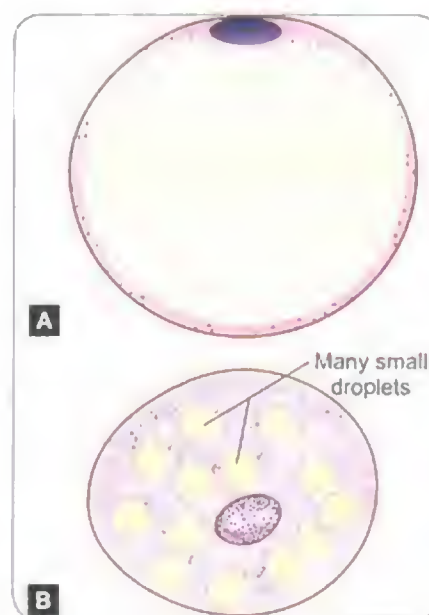
Adipose Tissue (Fat Cells)

1. White adipose tissue

- White (yellow) adipocytes are large in size and called **unilocular** since their cytoplasm is filled with a single large lipid droplet; nucleus is flat and pushed to periphery; mitochondria are few.
- Found in adults in **subcutaneous tissue**; **yellow bone marrow**; abdominal cavity within **peritoneal folds** and **around kidneys**.
- Acts as a storehouse of energy.

2. Brown adipose tissue

- Brown adipocytes are small polygonal cells and are called **multilocular** since their cytoplasm is filled with multiple lipid droplets; nucleus is in centre and cell organelle are spread out; numerous mitochondria containing iron containing pigment cytochromes are present (imparts brown color to these adipocytes).
- MC found in fetus and newborns; In infants **brown adipose tissue** contains a protein called **thermogenin** which releases heat.
- It is seen in **interscapular region, supraclavicular fossa, neck, mediastinum, and abdomen (para-aortic; peri-hepatic; paracolic, suprarenal; perihilar)**
- It is also abundant in hibernating animals.



Figs. 2.5A and B: (A) Unilocular adipose tissue (white adipose tissue cell); (B) Multilocular adipose tissue (brown adipose tissue cell) (Schematic representation)

CARTILAGE

Types of Cartilage

Hyaline Cartilage

Most abundant and common

- All long bones (except clavicle) are preformed in hyaline cartilage (endochondral ossification)
- Tendency to calcify > 40 years (except **articular cartilage**)
- All hyaline cartilages are covered by perichondrium **except articular cartilages**.
 - Articular cartilage
 - Thyroid cartilage
 - Larynx (**arytenoid lower end, cricoid**)
 - Nasal cartilage
 - Costal cartilage
 - Embryonic cartilage
 - Tracheal and bronchial cartilage ("AT LaNCET")

Elastic Cartilage

- Highly **flexible** due to elastic fibres
 - External ear/pinna
 - External auditory canal
 - Eustachian/auditory tube
 - Epiglottis, corniculate, cuneiform, apex of arytenoid cartilage
 - Inlet of larynx

Fibrocartilage

- Cartilage matrix with **type 1 collagen fibres** to withstand stress
 - Intervertebral discs
 - Symphysis pubis
 - Menisci
 - Sternoclavicular joint
 - Temporomandibular joint
 - Inferior radio-ulnar joint

EXTRA EDGE

- All cartilages are covered by perichondrium **except** articular cartilage and fibrocartilage.
- Hyaline cartilage is **blue**, elastic cartilage is **yellow** and fibrocartilage is **white**.
- Hyaline cartilage of respiratory tree extends upto bronchi.

BONE

Parts of a Long Bone

- Diaphysis:** Shaft of bone; **longest** and **strongest** portion of bone; **first part** to ossify; contains tubular **bone marrow cavity** in the centre.
- Metaphysis:** Epiphyseal end of diaphysis; richly supplied by 'hair pin' bends of arteries; area of **maximum**

growth velocity in bone; **most vascular part** of bone-prone to **avascular necrosis**; MC site for **hematogenous osteomyelitis**.

- Epiphyseal plate:** Cartilaginous plate responsible for **linear growth** (growth in length) of bone.
- Epiphysis: Growing end of the bone;** At the epiphyseal plate, new bone growth occurs by process of **endochondral ossification**.

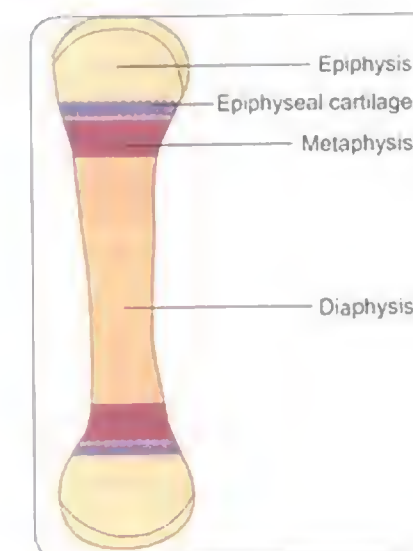


Fig. 2.6: Parts of a long bone

Microscopic Structure of Bone

- Compact (cortical) bone** consists of **Haversian system (osteon)**—consists of **concentric lamellae** of collagen surrounding central Haversian canal. **Haversian canal runs parallel** to axis of long bone and these communicate with each other through **Volkman's canals** which run perpendicular to axis of long bone.
- Cancellous (spongy) bone:** does NOT contain Haversian system.

Ossification of Bones

Intramembranous ossification	Endochondral ossification
Bone develops directly from osteogenic cells of the mesenchyme. Examples are: <ul style="list-style-type: none"> Cranial and facial bones Clavicle Mandible 	Pre-existing hyaline cartilage of bone is gradually replaced by bone; appositional growth . Examples: <ul style="list-style-type: none"> Most long bones are formed in this way

- Primary centre** of ossification usually appears **before birth** (exceptions—*os cuneiformis* and *os navicularis*).

- **Secondary centre** appears **after birth** (exceptions- lower end of femur and upper end of tibia).

Growth of a Long Bone

- **Appositional growth:** Increase in diameter of the long bones.
- **Endochondral growth:** Increase in length of long bones.
- **Law of union of epiphysis:** The epiphysis which begins to ossify first unites with the diaphysis (shaft) last and vice-versa (except **lower end of fibula**)
- In the "zone of hypertrophy", the chondrocytes mature and hypertrophy and secrete alkaline phosphatase.



Fig. 2.8: Milking cow position showing direction of nutrient foramina.

Growing end of long bones

- Growing end of long bones is always directed **apposite to the direction of nutrient foramen**.
- The direction of nutrient foramen is easily remembered by the dictum: "**Ta the elbow I go and from the knee I flee**". In the "milking cow" position, the direction of nutrient foramina is always downwards.
- Thus In upper limb, upper end of humerus and lower end of radius and ulna are growing ends. In lower limb the lower end of femur and upper end of tibia and fibula are the growing ends.

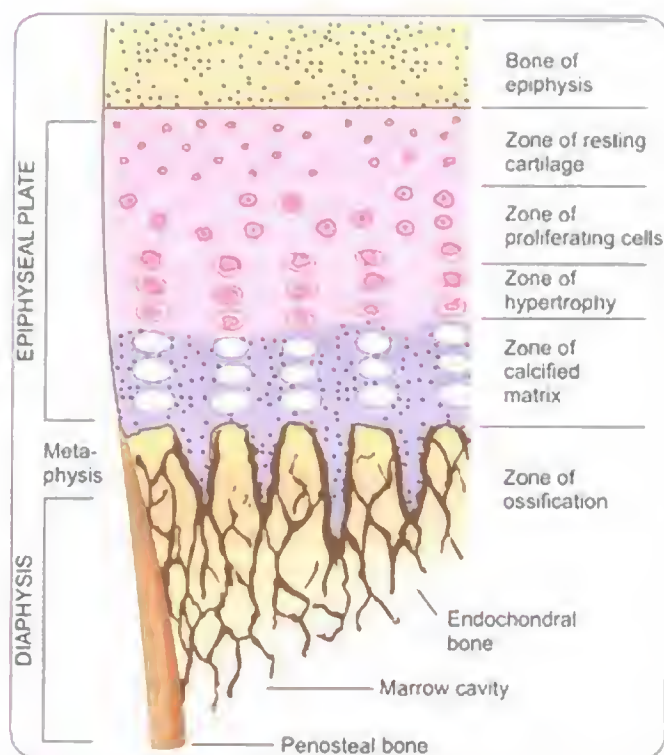
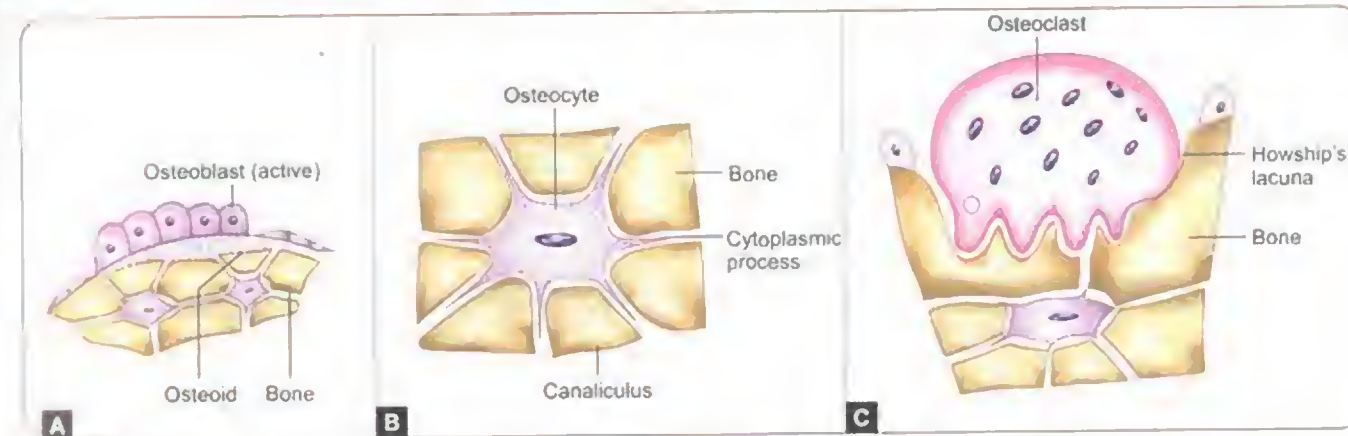


Fig. 2.7: Structure of an epiphyseal plate

Components of a Bone

- **Osteoprogenitor cells:** least differentiated bone forming cells; they are present in cellular layers of endosteum and periosteum; they are **stem cells of the bone** since they turn into osteoblasts; has well developed rough endoplasmic reticulum, mitochondria and Golgi complex.
- **Osteoblasts:** bone forming cells; it is a round cells with **single nucleus** and highly basophilic cytoplasm; it is rich in alkaline phosphatase; **BMP7** and **BMP2** (bone morphogenic protein) stimulate osteoblast differentiation; osteoblasts have **neuropeptide receptors**.
- **Osteocytes:** these are **mature form of osteoblasts**; the protoplasmic processes of adjacent osteocytes meet each other inside canaliculi and provide pathway for transport of nutrients; they account for **majority of cells** in the bone.
- **Osteoclasts:** these are **macrophages** of bone tissue and are derived from blood monocytes; they are **largest bone cells**; **multinucleated** and have **abundant lysosomes** rich in **acid phosphatase**-hence intensely **eosinophilic**; multiple cytoplasmic processes and lysosomes are found along the border where the osteoclast comes in contact with bone-called "**ruffled border**"-this is to **destroy** the bone and create a depression in the bone called "**Howship's lacuna**" or **resorption bay** in which the osteoclast resides. Activity of osteoclasts is controlled by calcitonin and parathormone.
- **Mnemonic:** Osteoblasts Build bone; Osteoclasts Crush bone
- Inorganic bone matrix in the form of **hydroxyapatite** $\{Ca_5(PO_4)_3OH\}$ accounts for **75% of bone mass**.
- Main collagen in **bone** is type 1 (type one)



Figs. 2.9A to C: Bone cells (A) Osteoblast on bone surface; (B) Osteocyte in lacuna; (C) Osteoclast in Howship's lacuna

Sesamoid bones

These are bones developing in muscle tendons.

- **Patella** in **quadriceps femoris** tendon-**largest** sesamoid bone in the body.
- **Fabella** in **lateral head of gastrocnemius**.
- **Cyamella** within tendon of **papliteus**.
- **Pisiform** in tendon of **flexor carpi ulnaris**.
- In the **distal portion of first metacarpal bone** (2 bones) (within tendons of **flexor pallicis brevis** and **adductor pollicis**).
- In the **distal portion of first metatarsal bone** (2 bones) (within tendon of **flexor hallucis brevis**-**hallux sesamoids**)
- In the ear, the **lenticular process of incus** is a sesamoid bone and is therefore considered the **fourth ossicle of middle ear**.
- **Rider's bone** in tendon of **adductor longus**.
- **Os peroneum** in tendon of **peroneus longus**.

- Tuberosity/tubercle of humerus
- Mastoid process

Aberrant epiphysis

- When a bone has one epiphysis, an occasional separate epiphysis may be present
- Head of 1st metacarpal
- Base of other metacarpals

EXTRA EDGE

- Total number of bones in body = **206**.
- **Pneumatic bones:** Air filled bones = Maxilla, Frontal, Ethmoid and Mastoid.
- **Sharpey's fibres:** Extension of fibres from the tendon into the outer layers of compact bone are called Sharpey's fibres.
- **Hilton's law:** the nerve supplying a joint also supplies the muscles that move the joint and the skin covering the insertion of such muscles.
- The part of the bone that is **most affected by osteoporosis** is **spongy bone**.

Types of Epiphysis

Pressure epiphysis

- Helps in transmission of body weight and protection of epiphyseal cartilage
- Head of femur
- Head of humerus
- Condyles of humerus and tibia

Atavistic epiphysis

- Separated in evolutionary phases
- Posterior tubercle of **talus** (os trigonum)
- Coracoid process of **scapula**

Traction epiphysis

- Caused by pull of muscles to withstand the pull
- Trochanters of femur

Bone Markers

Bone formation markers

- Serum total **alkaline phosphatase**
- Serum bone-specific alkaline phosphatase
- Serum osteocalcin
- Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP

Bone resorption markers

- Urinary hydroxyproline
- Urinary total pyridinoline (PYD)
- Urinary collagen type 1 cross-linked N-telopeptide (NTX)
- Urinary free deoxypyridinoline (DPD)
- Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
- Bone sialoprotein (BSP)
- Tartrate-resistant acid phosphatase

JOINTS

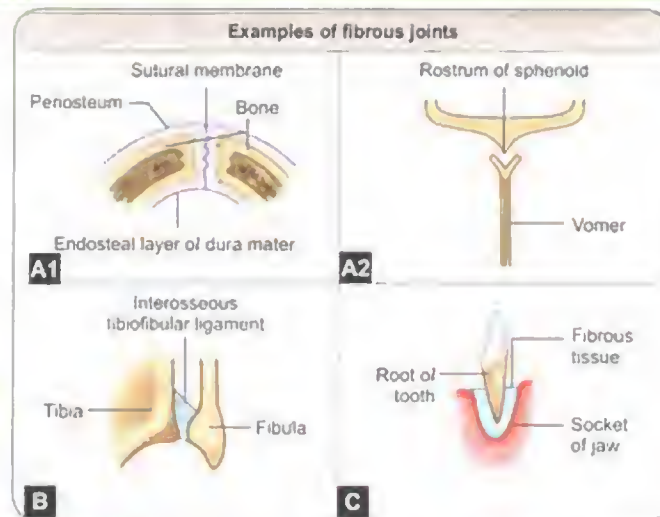
Functional Classification of Joints

- **Synarthroses** (immovable joints) show no mobility; ex: cranial sutures in adults, primary cartilaginous joints in children

Fibrous Joints

Fibrous Joints

- Sutures** Are limited to the **skull** and are **immovable**
- **Plane** suture: intranasal, median palatine suture.
 - **Serrate/limbous** suture: sagittal (interparietal) suture
 - **Denticulate** suture: **LAMBdoid** suture (**PARieTo-occipital**) suture ("LAMB **P**ARTies with **OCC**, ox!!"); **coranal (fronto-parietal)** suture
 - **Squamous** suture: temporo-parietal suture
 - **Schindylesis**: **ridged bone fits into a groove** on the other- junction between the **vomer and rostrum of sphenoid bone**.
- Gomphosis** (**Peg and socket** joint) such as a **tooth** in its socket.
- Syndesmosis** Closely apposed bony surfaces are bound together by an **interosseous ligament**, e.g. **inferior tibiafibular joint**.

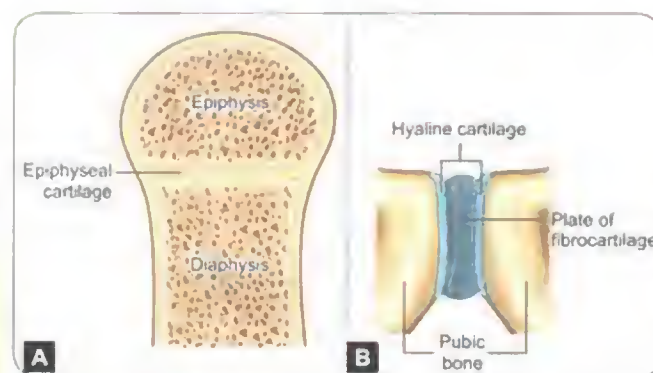


Figs 2.10A to C: Subtypes of fibrous joints (A) Suture; A1. Serrate type of suture; A2. Wedge and groove suture or schindylesis; (B) Syndesmosis; and (C) Gomphosis

Cartilaginous Joints

Cartilaginous Joints

- Synchondroses** (primary cartilaginous joints) Joints where bones are joined by plate of **hyaline cartilage**; these are **immovable** and **temporary** and once growth ceases they undergo **synostosis** (i.e. plate of hyaline cartilage is completely replaced by bone). Examples:
- Between **epiphysis and diaphysis** in the immature post-cranial skeleton
 - **Spheno-occipital** joint
 - **First costa-sternal/chandra-sternal** joint (it is actually a synarthrosis)
- Symphysis** (secondary cartilaginous joints) Joints where the articulating surfaces are covered by a thin layer of hyaline cartilage and **united by a disc of fibrocartilage**; these joints are **midline joints** and **permanent**. Example:
- **Symphysis pubis**
 - **Manubriosternal joint**
 - **Intervertebral** joints between vertebral bodies
 - **Sacroccygeal joint**.



Figs. 2.11A and B: Subtypes of cartilaginous joints (A) Primary cartilaginous joint or synchondrosis; (B) Secondary cartilaginous joint or symphysis

Synovial Joints

- Synovial joints are the **most evolved and most mobile joints**;
 - They possess **joint cavity** and **articular surfaces**
 - Are surrounded by a **fibrous capsule**;
 - Articular surface is surrounded by thin plate of articular cartilage.
 - The joint cavity is filled with **synovial fluid**-acts as lubricant and provides nutrition to articular cartilage
 - Synovial joints are also called "**diarthrodial**" freely mobile joints.
- Articular cartilage
 - Articular cartilage of all synovial joints in body is **hyaline cartilage** except those of **temporomandibular, sternoclavicular and acromioclavicular** joints which are fibrocartilage.
 - Articular cartilage is **avascular, non-nervous** and **devoid of perichondrium**
 - It **does NOT** have the capacity to repair or regenerate
 - It provides **slippery surfaces** for free movements.
- Based on movements, synovial joints maybe classified as below:
 - **Uni-axial joints** = movements occur around a single axis
 - **Bi-axial** = movements occur around two axes
 - **Tri-axial** = movements occur around three axes.

Types of Synovial Joints and Their Examples

Plane joint

- Intermetatarsal joints
- Some Intercarpal joints
- Sternoclavicular joint, acromioclavicular joint
- Superior tibiofibular joint

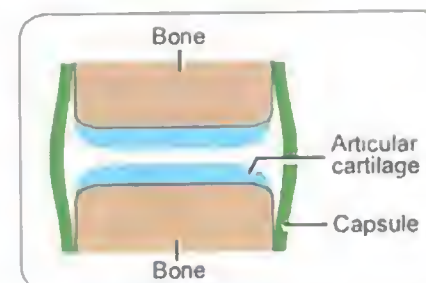


Fig. 2.12: Structure of a plane joint

Hinge joints (ginglymi) (Uni-axial)

Types of Synovial Joints and Their Examples

- Elbow joint
- Ankle joint
- Interphalangeal joint

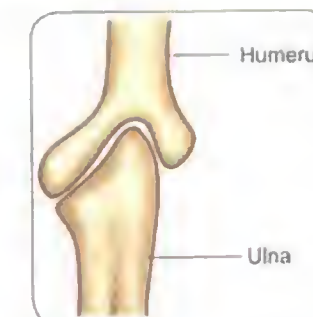


Fig. 2.13: Hinge joint.

Pivot (trochoid) joints (Uni-axial)

- Superior and Inferior radio-ulnar joint
- Median atlanto-axial joint

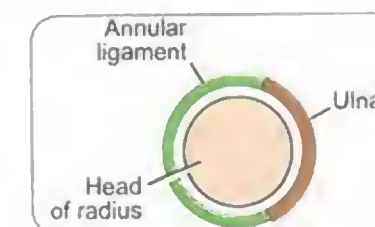


Fig. 2.14: Two examples of pivot joints. Superior radioulnar joint

Bicondylar joints (Uni-axial)

- Knee joint (largest joint, compound variety)
- Temporomandibular joint

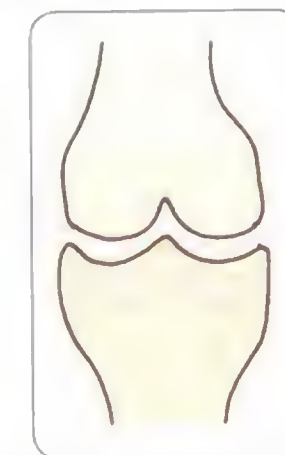


Fig. 2.15: Scheme to show a condylar joint

Ellipsoid joints (Bi-axial)

Contd...

Contd...

Contd...

Types of Synovial Joints and Their Examples

- Radiocarpal joint (wrist)
- Atlanto-occipital joint

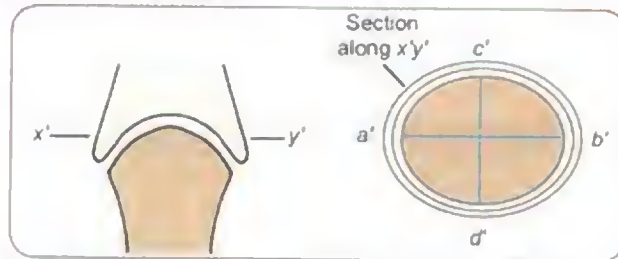


Fig. 2.16: Scheme to show the features of an ellipsoid joint

Condylloid joint (Bi-axial)

- Metacarpophalangeal joint

Saddle(sellar) joints (Bi-axial)

- First Carpometacarpal joint of thumb
- Calcaneocuboid joint
- Incudo-Malleolar joint (smallest saddle joint); "I'M sad!"



Fig. 2.17: Scheme to show a saddle joint

Spheroidal (ball and socket) joints (tri-axial)

- Tale-calcaneo-navicular joint
 - Hip joint
 - Incudo-Stapedial joint
 - Shoulder joint
- Mnemonic: "THIS" (Also, 'IS' in 'THIS' = Incudo-Stapedial!)

MUSCLES

Composite muscles	Digastric muscles	Subcutaneous muscles	Cruciate muscles
Muscles which have Innervations from 2 different nerves or 2 different embryological counterparts but have the same function:	Muscles with 2 bellies (or 2 heads) with 2 different origins:		Muscles in which fasciculi are crossed:
<ul style="list-style-type: none"> • Pectineus • Adductor magnus • Biceps femoris • Quadriceps femoris • Digastric • Iliopsoas • Flexor digitorum profundus 	<ul style="list-style-type: none"> • Occipitofrontalis • Omohyoid • Digastric • Rectus femoris • Gastrocnemius • Sterno-cleidomastoid 	<ul style="list-style-type: none"> • Platysma • Dartos • Palmaris brevis • Subareolar muscles of Nipple • Muscles of scalp • Corrugator cutis ani 	<ul style="list-style-type: none"> • Sternocleidomastoid • Masseter • Adductor magnus

Note: Further anatomy of smooth, skeletal and cardiac muscles and nerve anatomy are discussed under muscle and nerve physiology in physiology section.

Contd...

Types of Synovial Joints and Their Examples

Fig. 2.18: Ball and socket joint.

EXTRA EDGE

- **Compound joint** is where more than two bones take part in formation of the joint. Ex: *Knee, ankle, elbow, wrist*.
- **Complex joint**: where the joint cavity is divided into two compartments by an **articular disc or meniscus** (ex: *knee* has menisci; *T-M joint* and *sternoclavicular joint* contains **articular disc**).
- **Spheroidal (ball and socket) joints** show **greatest range of movement** among all synovial joints.
- **Metacarpophalangeal joints** are ellipsoid joints but structurally they belong to **condylloid joints**.

Synovial Cells**Type A synoviocytes**

- Most numerous,
- Resemble macrophages, and contain numerous lysosomes and extensive Golgi apparatus

Type B synoviocytes

- Are specialized **fibroblasts**
 - **Secrete Synovial fluid**
- Contain abundant **rough endoplasmic reticulum** that is consistent with their secretory function

Fascicular Arrangement of Muscles

- **Muscles with parallel fasciculi**: the fasciculi are parallel to the line of pull and these muscles have a greater range of movement. **Examples** are:
 - Quadrilateral: thyrohyoid
 - Strap-like: *sartorius* and sternohyoid
 - Strap-like with tendinous insertions: rectus abdominis
 - Fusiform: biceps brachii, digastric
- **Muscles with oblique fasciculi**: this arrangement makes the muscle more powerful; but range of movement is limited. **Examples** are:
 - Triangular: Temporalis, adductor longus
 - Unipennate: Flexor pollicis longus, extensor digitorum longus
 - Bipennate: rectus femoris, flexor hallucis longus
 - Multipennate: *tibialis anterior*, subscapularis, deltoid (acromial fibres).

ANASTOMOSIS**Actual Anastomosis**

- End to end anastomosis: when arteries join end to end.
 - **Examples**: labial arteries, facial arteries, palmar arch, plantar arch, circle of Willis, uterine and

ovarian arteries, intestinal arcades around the stomach.

- **Convergent anastomosis**: when two arteries converge and join to form a larger artery.
 - **Example**: two vertebral arteries unite to form a larger basilar artery.

Potential Anastomosis

- This takes place between terminal arterioles. In such type of anastomosis, collateral circulation cannot take place immediately if one of the artery is suddenly blocked. However if sufficient time is given, the arterioles can dilate and establish collateral circulation.
 - **Examples**: coronary arteries, arteries around limb joints, the cortical branches of cerebral arteries etc.

End Arteries

- These are arteries whose branches DO NOT anastomose with branches of other adjacent arteries. If these arteries are blocked, the area suffers from **ischemia** that may lead to **cell necrosis**. **Examples**:
 - Central retinal artery
 - Central (medullary) branches of cerebral arteries
 - Arteries of spleen, liver, kidneys and metaphyses of long bones.

UPPER LIMB**BONES AND JOINTS OF UPPER LIMB****CLAVICLE**

- It is the **1st bone in the body to ossify** (between 5th and 6th week of intrauterine life)
- **Clavicle is the ONLY LONG BONE**:
 - Which **ossifies in membrane**;
 - Which has **2 primary centres of ossification**;
 - Which **lies horizontally**.
 - Which has **NO medullary cavity** and
- It is **subcutaneous throughout** and maybe pierced by a cutaneous nerve (**intermediate supraclavicular nerve**).
- The clavicle is often fractured at the junction of medial 2/3 and lateral middle 1/3 this is its **weakest** part.

More High Yield about Clavicle

- Clavicle is the **collar bone**; (Latin, *clavicula* = small key!)
- **Clavicular fracture** is the **MC birth fracture** (esp. during breech delivery).

- **Absent distal end of clavicle** is seen in: Cleidocranial dysostosis; Rheumatoid arthritis; Hyperparathyroidism; Multiple myeloma; Pyknodysostosis

SCAPULA

- **Margins of the scapula**:
 - **Superior margin**: thin and sharp and has supra-scapular notch that is converted into a foramen by transverse scapular ligament. Suprascapular **Artery** passes above the ligament and suprascapular **Nerve** passes below it (through the suprascapular foramen)-Mnemonic: "**AR**my above **N**avy!"
 - **Lateral margin**: **thickest**
 - **Medial/vertebral margin**
- **Angles of the scapula**: The three corners of the scapula are called 'angles'-superior, inferior and lateral angle.

- The **lateral angle** (a.k.a **glenoid angle**) is the thickest and sometimes called '**head of the scapula**'.
- **Superior angle**-opposite T2 spine
- **Base/root of spine of scapula**-opposite T3 spine.
- **Inferior angle**-opposite T7 spine
- **Processes of the scapula:**
 1. **Coracoid process** (crow's beak):
 - Tip gives origin to **coracobrachialis medially** and **short head of biceps laterally**;
 - **Upper surface** receives insertion of **pectoralis minor**.
 2. **Spine of the scapula**: shelf like projection from dorsal surface.
 3. **Acromion**: projects from the lateral end of spine of scapula.
- **Attachments on scapula:**
 - **Supraglenoid tubercle** gives origin to **Long head of Biceps** and **Infraglenoid tubercle** gives origin to **Long head of Triceps**. (She Loves Baking; I Love Taking!)
 - **Ventral surface medial margin**-insertion of serratus anterior
 - **Dorsal surface medial margin**-from above below insertions of levator scapulae, rhomboideus minor and rhomboideus major.

Movement of scapula	Muscles responsible
Retraction	Rhomboid major and Rhomboideus minor Trapezius (middle fibres)
Protraction	Serratus anterior Pectoralis minor
Elevation	Levator scapulae Trapezius (upper fibres)
Depression	Pectoralis minor Trapezius (lower fibres)

EXTRA EDGE

- Scapula is a.k.a **shoulder blade**.
- **Congenital high scapulo** (scapula elevala) is called **Sprengel's shoulder**-a/w rib abnormalities; cervical/thoracic scoliosis and Klippel Fiel syndrome (congenital fusion of cervical vertebrae).
- Scapula ossifies from one primary center and 7 secondary centers.

HUMERUS

- Upper end has head, neck and tubercles.
- Neck of humerus:

- **Anatomical** of humerus: a slight constriction that demarcates the head from rest of the upper end of humerus.
- **Surgical neck** of humerus: between the upper end and shaft. Vulnerable to fracture leading to damage of axillary nerve and posterior circumflex humeral vessels.
- **Tubercles:**
 - **Greater tubercle**: projects from lateral part of upper end; **Attachments** on greater tubercle: insertions of **supraspinatus**, **infraspinatus** and **teres minor** from above downwards
 - **Lesser tubercle**: projects anteriorly from upper end.; **subscapularis** insert on lesser tubercle.

Intertubercular sulcus (bicipital groove)

- It lies in between the greater and lesser tubercles-contains the **tendon of long head of biceps brachii** and **ascending branch of anterior circumflex humeral artery**.
- Its lateral lip provides insertion to **pectoralis major** and medial lip to **teres major**; floor provides insertion to **Latissimus Dorsi**.
- Mnemonic: "A LaDy between two majors!"

- **Radial groove (spiral groove)** is present on the posterior surface of humerus; contains the **radial nerve** and **profunda brachii** vessels.
- The **shaft of the humerus** is cylindrical in upper half and triangular in cross section in lower half.
- **Medial epicondyle:**
 - Posterior surface of **medial epicondyle** has groove lodging **ulnar nerve**-sometime called "**funny bone**" since tapping here results in tingling sensation-you would have felt it if you have hanged your elbow anywhere!.
 - Anterior aspect of medial epicondyle present the **common flexor origin** for five muscles (pronator teres, flexor carpi radialis, palmaris longus, flexor carpi ulnaris and humeral head of flexor digitorum superficialis).
- **Lateral epicondyle**: its anterior surface presents **common extensor origin** for 4 muscles (extensor digitorum, extensor carpi radialis brevis, extensor carpi ulnaris and extensor digiti minimi) below which it gives origin to **supinator**. Its posterior surface gives origin to **anconeus**.
- 3 nerves directly related to the humerus and therefore liable to injury: the **axillary N.** at the **surgical neck**, the **radial N.** at the **radial groove** and the **ulnar N.** behind the **medial epicondyle**.

EXTRA EDGE

- The humerus also ossifies from 1 **Primary** and 7 **Secondary** centres (P7S). (just like the scapula).
- Growing end of the hUmerUs is the **Upper** end; (femur-lower end).
- **Angle of humeral torsion is 164** degrees (Angle of femoral torsion is ~ 15 degrees).
- **Supracondylar spur** is a small hook like process occasionally present on **anteromedial** surface of shaft of humerus, 5 cm above medial epicondyle; if it is attached to the medial epicondyle by **ligament of Struthers** (third head of coracobrachialis), a foramen is created through which median nerve and brachial artery pass.

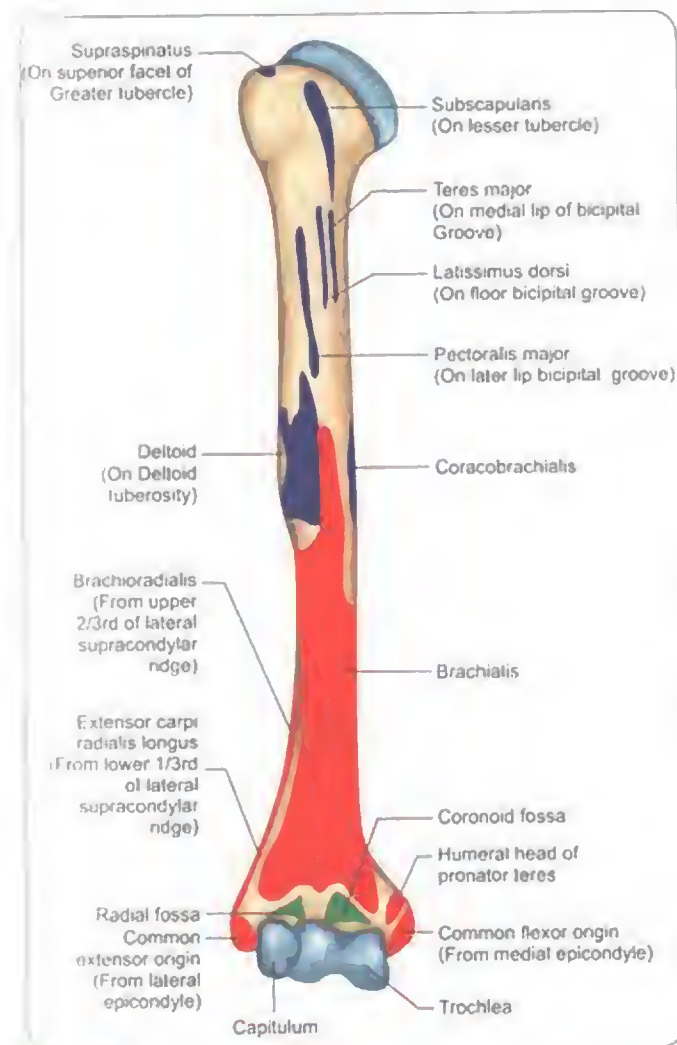


Fig. 2.19: Features of humerus and muscles attached to right humerus on anterior aspect

RADIUS

- Radius is the **lateral** bone; it is **weight bearing** and hence **more prone to fractures** compared to ulna.
- The head of radius moves inside the **annular ligament** during pronation and supination of forearm at the superior radioulnar joint.
- **Lister's tubercle** (dorsal radial tubercle) is seen at posterior aspect of lower end and can be palpated in line

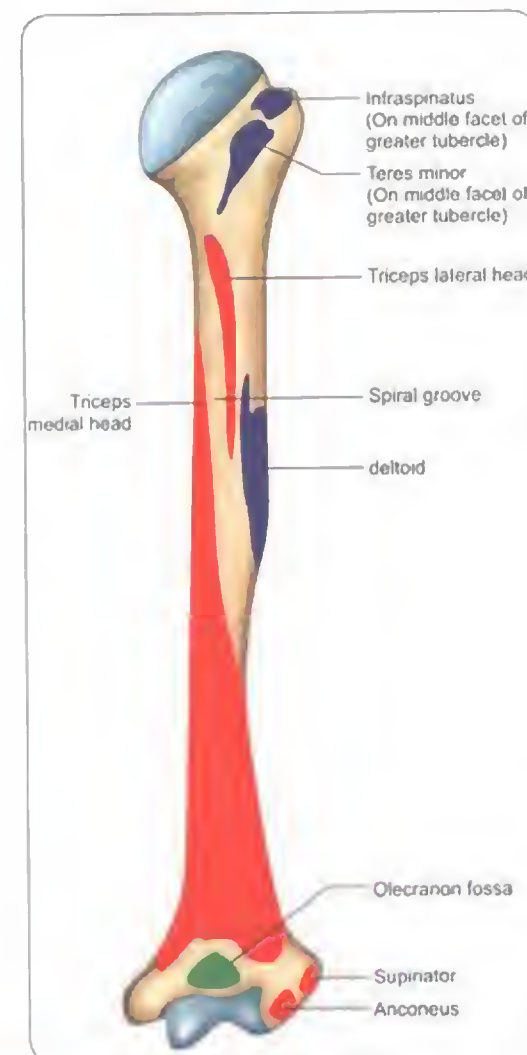


Fig. 2.20: Muscles attached to posterior surface of right humerus

- with the cleft between the index and middle fingers. The groove medial to Lister's tubercle is traversed by tendon of extensor pollicis longus (EPL) and groove lateral to it by ECRB and ECRL.
- Muscles of **pronation** (pronator teres and pronator quadratus) and **supination** (biceps brachii and supinator) are inserted into the radius.
- **Brachioradialis** inserts onto the base of **styloid process of radius**.

- **Because** the radial styloid process extends farther distally than the ulnar styloid process, the **hand can be adducted to a greater degree** than it can be abducted!

ULNA

- Ulna is the medial bone.
- The upper end has two **processes** (**olecranon** and **coronoid**) and two **natches** (**radial** and **trochlear**).
- The annular ligament is attached to the anterior and posterior margins of the radial notch of the ulna.
- Supinator fossa on the lateral surface gives origin to supinator muscle.
- **Growing ends** of both radius and ulna are the **distal ends**.



Figs. 2.21: Pediatric elbow showing CRITOE which gives the order of appearance of ossification centers in the bony parts around elbow joint:— Capitulum—first year, Radial head—3-4 years, Internal or medial epicondyle—5-6 years, Trochlea—7-8 years, Olecranon process—9 years, External or lateral epicondyle—11 years

CARPAL BONES

- **Proximal row** (from lateral to medial side): **Scaphoid**, **Lunate**, **Triquetral**, **Pisiform** ("**She Looks Too Pretty**").
- **Distal row** (from lateral to medial side): **Trapezium**, **Trapezoid**, **Capitate**, **Hamate** ("**Try To Catch Her**").
- **Scaphoid:**
 - Boat shaped
 - **MC fractured** of the carpal bones; MC through **waist** of scaphoid; **proximal half** can undergo **avascular necrosis**.
 - Scaphoid tubercle can be palpated in the floor of anatomical snuff box—gives attachment to flexor retinaculum.

- **Lunate:**
 - **Half moon** shaped
 - **MC dislocated** of the carpal bones
 - Dislocates anteriorly and injures median nerve inside the carpal tunnel.
- **Triquetral:** **pyramidal** in shape
- **Pisiform**
 - **Pea** shaped;
 - It is a sesamoid bone lying within the tendon of the **Flexor carpi ulnaris**;
 - BOTH flexor and extensor retinaculum are attached to the pisiform;
 - Pisiform articulates with **ONLY** one other carpal bone—the **triquetral**
- **Trapezium:** **quadrilateral** in shape; forms first carpometacarpal joint (thumb).
- **Capitate:** **Largest** carpal bone; articulate with third metacarpal bone.
- **Hamate:**
 - Has a **Hook** that is in contact with **deep branch of ulnar nerve**;
 - Medial side of hook gives attachment of **flexor digiti minimi**.
- Remember: Lateral bones of both rows (scaphoid and trapezium) and medial bones of both rows (pisiform and hamate) give attachment to flexor retinaculum.

Ossification of carpal bones

- The carpal bones are usually **cartilaginous at birth** and ossify starting from first year of life.
- All carpal bones ossify from **single centre** only.
- **Carpal bone to ossify first = Capitate** (2 months) and the **last to ossify = Pisiform** (**12 years**) ("**Caterpillar**").
- Other bones: please see figure

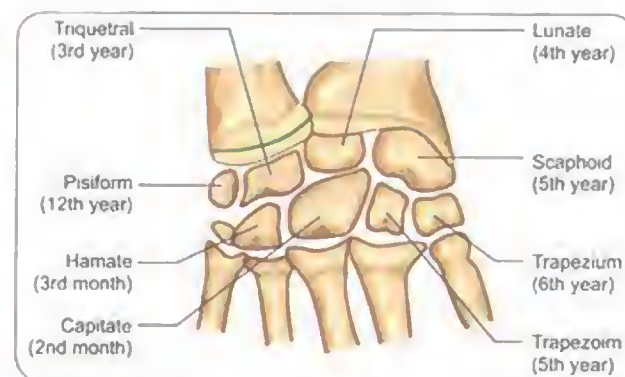


Fig. 2.22: Time of appearance of ossification centers of carpal bones

Metacarpal Bones

- Five metacarpals are numbered from **lateral to medial** side.
- **Unique features of first metacarpal** bone: it is **shortest and strongest**; it is the modified first phalanx of thumb; It is not in line with other four metacarpals as it is more anteriorly placed.

PECTORAL GIRDLE

The pectoral/shoulder girdle consist of two bones—clavicle and scapula and two joints—acromioclavicular and sternoclavicular joints.

Acromioclavicular Joint

- It is a **plane** synovial joint
- The **coracoclavicular ligament** is a very **powerful ligament** that **transmits the weight** of the upper limb to the **axial skeleton** (through the clavicle).

Sternoclavicular Joint

- It is a **saddle** type of synovial joint
- The main ligaments are **sternoclavicular** ligament, **interclavicular** ligament and **costoclavicular** ligament.
- **Posteriorly** the joint is related to the **brachiocephalic veins and trachea** on both sides and **brachiocephalic artery** (on right side).

SHOULDER JOINT

- **Most mobile** joint in the human body.
- It is a **multi-axial, ball and socket** type of **synovial joint** between the scapula (glenoid fossa) and the head of the humerus (hence **gleno-humeral** joint).
- The head of the humerus is much larger than the glenoid fossa, giving the joint inherent instability. To reduce the disproportion in surfaces, the glenoid fossa is deepened by a **fibrocartilage** rim, called the **glenoid labrum**.

Stabilisers of the Shoulder Joint

Static Stabilisers	Dynamic Stabilisers
<ul style="list-style-type: none"> • Glenohumeral ligaments • Glenoid labrum • Normal glenoid and humeral version • Negative intra-articular pressure 	<ul style="list-style-type: none"> • Muscles acting across the joint • Rotator Cuff muscles • Tendon of the long head of biceps • Periscapular muscles

Bursae

- **Subacromial (subdeltoid)** bursa—Located **between** supraspinatus tendon below and the coracoacromial

arch and deltoid above. It is a **NON-communicating** bursa and the **largest bursa** in the human body. This bursa acts as a **secondary socket** for humeral head during hyper-abduction.

- **Subscapular** bursa—Located between the **subscapularis tendon** and the scapula. It is the **ONLY communicating** bursa, which is **always present**.
- **Infraspinatus** bursa: between the tendon of infraspinatus and joint capsule.

Ligaments

- **Glenohumeral** ligaments (superior, middle and inferior)—Consists of three bands, which runs with the joint capsule from the glenoid fossa to the anatomical neck of the humerus. They act to **stabilise the anterior aspect** of the joint.
- **Coracohumeral** ligament—Attaches the base of the coracoid process to the greater tubercle of the humerus. It **supports the superior part** of the joint capsule.
- **Transverse humeral** ligament—Spans the distance between the two tubercles of the humerus. It **holds the tendon of the long head of the biceps** in the intertubercular groove.
- **Coracoacromial** ligament: runs between the acromion and coracoid process of the scapula, forming the coraco-acromial arch. This structure overlies the shoulder joint, **preventing superior displacement of the humeral head**.

Neurovascular Supply

- **Nerves:** Axillary, subscapular and lateral pectoral nerves (all derived from C5,6). Thus an **upper brachial plexus injury (Erb's palsy)** will affect shoulder joint function.
- **Blood supply:**
 - Anterior and posterior circumflex humeral artery (form **anastomosis around surgical neck** of humerus)
 - Suprascapular artery
 - Circumflex scapular artery

Movements of Shoulder

Movements	Muscle responsible
Abduction	0–15 degrees by supraspinatus; 15–90 degrees by deltoid; hyperabduction above 90 degrees (overhead abduction) by trapezius and serratus anterior
Adduction	Pectoralis major, latissimus dorsi and teres major

Contd...

Contd...

Movements	Muscle responsible
Flexion	Clavicular head of pectoralis major; Anterior fibres of deltoid and coracobrachialis
Extension	Posterior fibres of deltoid, teres major and latissimus dorsi
Medial rotation	Pectoralis major; teres major, latissimus dorsi and subscapularis
Lateral rotation	Infraspinatus, teres minor and posterior fibres of deltoid

EXTRA EDGE

- In traumatic anterior dislocation of shoulder joint, **inferior glenohumeral ligament** is stretched or its attachment to the labrum is torn-**Bankart's lesion** which predisposes to recurrent dislocation of shoulder joint.
- In **subacromial bursitis**, pressure over the deltoid just below the acromion elicits pain, BUT pain cannot be elicited after abduction (since the bursa is now under the acromion!)-**Dawborn's sign**.
- Axillary nerve** is injured in anterior dislocation of shoulder joint.

ELBOW JOINT

- A **hinge** type of synovial joint, and a **compound joint** (since more than 2 bones take part).
- Articulating surfaces:
 - **Humero-ulnar**: trochlea of the humerus with trochlear notch of the ulna.
 - **Humero-radial**: capitulum of the humerus with the concave upper surface of head of radius
- Ligaments**:
 - **Ulnar collateral ligaments**-has anterior, posterior and transverse bands.
 - **Radial collateral ligament**
- Intra-articular fossae**: at the lower end of the humerus there are three fat filled fossae: coronoid fossa, radial fossa and olecranon fossa-these fossae lie **within the joint cavity**.
- Bursae**: Subcutaneous olecranon bursa; subtendinous olecranon bursa; Intratendinous olecranon bursa; bicipitoradial bursa.
- Blood supply**: from arterial anastomosis around it.
- Nerve supply**:
 - Radial nerve (through its branch to anconeus)
 - Musculocutaneous nerve (through its branch to brachialis)
 - Ulnar nerve and Median nerve.

Movements of Elbow

Movement	Muscles producing	Factors limiting
Flexion	Biceps brachii, brachialis and brachioradialis-assisted by pronator teres	Apposition of the forearm and arm
Extension	Triceps- assisted by anconeus	Straight position of the limb

EXTRA EDGE

- The **carrying angle** is the angle between the long axis of arm and forearm. Normal value is 10-15 degrees (slightly more in females). Carrying angle is **masked during flexion of the elbow** and more pronounced in the extended position.
- The joint surfaces of the elbow are in **maximum contact** when the forearm is **flexed to 90 degrees and semipronated** (natural position of the elbow while free or while engaged in activities)-this is the **position of greatest stability**.
- Olecranon bursitis** due to repeated pressure-**student's elbow/miner's elbow**.
- Fractured olecranon** is often referred to as "**fractured elbow**".
- Other eponymous elbow conditions like **golfer's elbow**; **tennis elbow**; **pulled elbow**; **three bony points of elbow** etc... are covered in **orthopedics chapter** (Pg 722).

RADIOULNAR JOINTS

- Both **superior and inferior radioulnar joints** are **pivot** type of synovial joints.
- Middle radio-ulnar joint** (**syndesmosis** type of fibrous joint) refers to the **interosseous membrane and oblique cord** connecting the radius and ulna.
- Both radioulnar joints allow **supination and pronation**.
- Pronation**: Mainly by pronator quadratus assisted by pronator teres.
- Supination**: Biceps brachii and supinator muscles.

WRIST JOINT

- Wrist joint is the **radio-carpal joint** since **ONLY** the radius articulates with the carpal bones-**scaphoid, lunate and triquetrum** from lateral to medial side.
- It is a **biaxial ellipsoid** joint.

Movements at Wrist Joint

- Flexion** (palmar flexion): by flexor muscles
- Extension** (dorsiflexion) by extensor muscles

- Abduction** (radial deviation): by ECRL and ECRB and FCR muscles.

Adduction (ulnar deviation): by Extensor carpi ulnaris and flexor carpi ulnaris muscles.

MUSCLES OF THE UPPER LIMB**MUSCLES OF THE BACK****Superficial Muscle of Back**

Origin	Insertion	Nerve Supply	Action
Levator scapulae			
Transverse processes of C1-C4 vertebrae	Medial border of scapula from the superior angle to the spine	Dorsal scapular nerve (C5)	Elevates the scapula
Rhomboides Major			
Spines of vertebrae T2-T5	Medial border of scapula inferior to spine of scapula	Dorsal scapular nerve (C5)	Retracts, elevates and rotates the scapula inferiorly
Rhomboides Minor			
Inferior end of ligamentum nuchae, spines of vertebrae C7 and T1	Medial border of scapula at root of spine of scapula	Dorsal scapular nerve (C5)	Retracts, elevates and rotates the scapula inferiorly

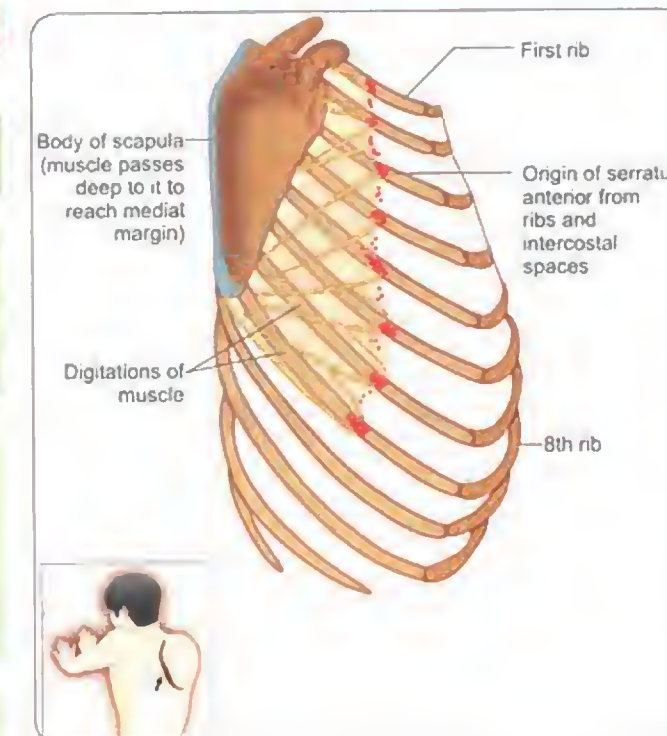


Fig. 2.23: Scheme to show the attachments of the serratus anterior

Trapezius

- Trapezius** is a flat **triangular** muscle; the **paired** trapezius muscles form a **diamond shape** from which the name 'trapezius' is derived!
- Supplied by: **spinal part of accessory nerve** (CN XI).
- Paralysis leads to **dropped shoulder**.
- Actions:
 - **Elevates scapula** (**shrugging muscle**)
 - Retracts scapula and **rotate the scapula during abduction** of the arm beyond 90 degrees.

Latissimus Dorsi

- Supplied by thoracodorsal nerve (C 6,7,8)
- Climbing** muscle (along with help of **pectoralis major**); also takes part in all **violent expiratory efforts** (**cough**).
- Action: **Adducts, extends** and **internally rotates** the arm.
- See attached figure for origin and insertion of trapezius and latissimus dorsi muscles-important MCQ information.

Serratus Anterior

- A.k.a boxer's muscle
- Origin: 8 digitations from **outer surface of upper 8 ribs**.
- Insertion: Costal surface of **medial border of scapula**.
- Supplied by N. to **Serratus Anterior**, **Long thoracic N. of Bell** (C5, 6, 7)-lesion leads to **Winging of Scapula**.
- Actions:
 - **Protracts** and **rotates scapula**;
 - **Upwards abduction of arm** (90-180 degrees)—("C5,6,7-raise your arms to heaven!")
 - It helps in **laboured inspiration**
- Serratus Anterior** is **pierced** while **tapping of pleural fluid** in mid-axillary line in 6th intercostal space

EXTRA EDGE

- **Latissimus dorsi** is also called '**swimmers muscle**' since it is used in *backstroke* in swimming. It is active in persons who use **crutches**. Its action can be tested by asking the person to **cough** and feel for its contraction.
- **Triangle of Auscultation:** A space on the back where the relatively thin musculature allows for respiratory sounds to be heard more clearly with a stethoscope. Corresponds to **sixth intercostal space**. Boundaries are:
 - Superiorly, by **Trapezius**
 - Inferiorly, by **Latissimus dorsi**
 - Laterally by **medial margin of the scapula**
 - Floor is partly formed by **Rhomboideus major**.
- **Lumbar triangle of Petit:** is bounded inferiorly by iliac crest; laterally (anteriorly) by free margin of external oblique and medially (posteriorly) by lateral margin of latissimus dorsi muscle. **Lumbar hernia** occurs through this triangle

MUSCLES OF SCAPULAR REGION

Deltoid

- **Origin:** V shaped origin

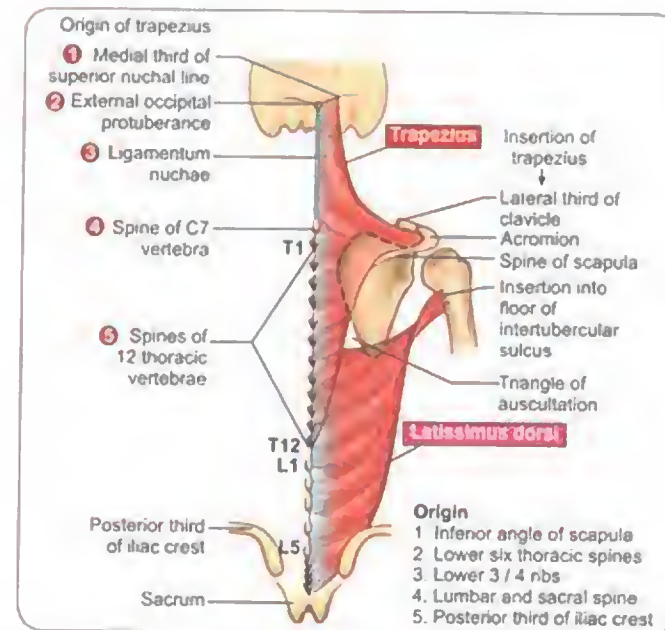


Fig. 2.24: Origin and insertion of trapezius and latissimus dorsi muscles

Other Muscles of Scapular Region

Origin	Insertion	Nerve Supply	Action
Supraspinatus			
Medial 2/3 of supraspinous fossa in the dorsal surface of the scapula	Greater tubercle of the humerus (uppermost impression)	Suprascapular nerve (C5,6) from upper trunk of brachial plexus	Abduction of arm (first 15 degrees); stabilises shoulder joint

Contd...

Contd...

Origin	Insertion	Nerve Supply	Action
Infraspinatus			
Medial 2/3 of infraspinous fossa in the dorsal surface of the scapula	Posterior aspect of upper end of humerus; middle impression on greater tubercle	Suprascapular nerve (C5,6) from upper trunk of brachial plexus	Adductor and lateral rotator of humerus
Teres Minor			
Upper 2/3 of lateral border of dorsal surface of scapula	Posterior aspect of upper end of humerus; lowest impression on greater tubercle	Axillary nerve (C5,6)	Adductor and lateral rotator of humerus (same as infraspinatus)
Teres Major			
Lower 1/3 of lateral border of dorsal surface of scapula	Anterior aspect of upper end of humerus, in medial lip of intertubercular sulcus (bicipital groove)	Lower subscapular nerve (C6,7) from posterior cord of brachial plexus	Adductor and medial rotator of the arm; MOST important stabiliser of head of humerus in the glenoid socket
Subscapularis			
Medial 2/3 of subscapular fossa on the costal surface of scapula	Lesser tubercle of the humerus	Upper and lower subscapular nerves (C5,6,7) from posterior cord of brachial plexus	Adductor and (most important) medial rotator of the arm

Muscles of Arm

Origin	Insertion	Nerve Supply	Action
Anterior Compartment			
Biceps brachii			
Long head from supraglenoid tubercle of scapula	Tuberosity of radius (posterior part)	Musculocutaneous nerve (C5,6,7)	Flexion of arm at shoulder (short head)
Short head from tip of coracoid process (together with coracobrachialis)			Flexion of forearm (at elbow)
Coracobrachialis			
Tip of coracoid process (in common with short head of biceps)	Medial border of humerus (near middle of shaft)	Musculocutaneous nerve (C5,6,7)	Flexor of arm
Brachialis			
Front of lower half of humerus	Anterior surface of coronoid process of ulna (including tuberosity)	Musculocutaneous nerve (C5,6,7)	Powerful Flexor of forearm at elbow joint
Intermuscular septa		Radial nerve (lateral part)	
Posterior Compartment			
Triceps brachii			
Long head from infraglenoid tubercle (of scapula)	Olecranon process of ulna	Radial Nerve (C6,7,8)	Major extension of forearm at elbow joint
Lateral head from ridge on posterior aspect of humerus			Long head helps in bringing back the abducted or extended arm to the side of the body
Medial head from posterior surface of humerus below the radial groove			

More Info about Arm Muscles

- **Brachialis** sustains the flexed position of the forearm since it is a very **powerful flexor**—hence called “workhorse of elbow flexors”.
- **Biceps brachii**
 - Although lying in anterior compartment of arm, biceps has no attachments to humerus.
 - Biceps is a “three joint muscle”—crosses the shoulder, elbow and superior radioulnar joints.
 - At least 8 small branches arise for the biceps muscle from the brachial artery.
- **Bicipital aponeurosis** (lacertus fibrosus):
 - A fibrous expansion that extends from medial side of biceps tendon and blends with deep fascia to attach to posterior border of ulna.
 - It prevents pressure accumulating within the biceps muscle during *pronation supination* movements.
 - **Median cubital vein** is related superficially to bicipital aponeurosis.
- **Triceps:**
 - The *medial head of triceps* is active during all types of extension and so is the ‘workhorse of forearm extension’.
 - The radial nerve is surgically exposed at spiral groove by *dividing the lateral head of triceps*.

EXTRA EDGE

- **Coracobrachialis** was called **Casser’s perforated muscle** since the **musculocutaneous nerve** pierces it.
- A small slip from the medial head of triceps is inserted into the capsule of elbow joint—called **articularis cubiti or subanconeus** muscle; it is the upper limb analog of the articularis genu (subcrureus) muscle of vastus intermedius of lower limb.
- Developmentally, **anconeus** is considered an extension of triceps muscle.
- Muscles **crossing both shoulder and elbow** are **biceps** and **long head of triceps**.

Muscles of Anterior Compartment of Forearm

- These are the **flexor-pronator** muscles and are arranged in 3 layers:
- Superficial layer:
 - Pronator teres
 - Flexor carpi radialis (FCR)
 - Flexor carpi ulnaris (FCU)

- Palmaris Longus
- Intermediate Layer:
 - Flexor digitorum superficialis (FDS)
- Deep Layer
 - Flexor digitorum profundus (FDP)
 - Flexor pollicis longus (FPL)
 - Pronator quadratus

Note

- For origin and insertion of individual muscles please refer an anatomy textbook. However, the most important MCQ points about these are given below.

High Yield MCQ Points about Anterior Forearm Muscles

- The superficial and intermediate layers muscles mentioned above cross the elbow joint but **deep layer does NOT**.
- The 4 superficial layer muscles mentioned above arise from **common flexor origin on medial epicondyle of humerus**.
- All anterior compartment muscles mentioned above are supplied by **Median nerve except FCU** and **medial half of FDP**.
- Deep layer of flexors (FDP, FPL) and are all supplied by anterior interosseous nerve
- **Pronator quadratus** is supplied by **anterior interosseous branch of median nerve**.
- At the wrist, radial artery lies **immediately lateral to tendon of flexor carpi radialis**.
- **Palmaris longus** may sometimes be **absent**.
- **Palmaris longus** tendon is used as **graft** for surgical repair of damaged flexor tendons in the hand.
- Ulnar nerve enters the forearm between two heads of origin of FCU—when it is compressed here it is called “**cubital tunnel syndrome**”.
- The **tendons** of the FDP muscle have a **split (Camper’s Chiasm; chiasma tendineum)** at the end of them through which the tendons of FDP pass.
- **FDP has dual nerve supply**—medial half from ulnar nerve and lateral half from median via anterior interosseous nerve
- **Radial bursa** is the synovial sheath surrounding the FPL tendon.
- **Ulnar bursa** is the common synovial sheath surrounding the tendons of **FDS and FDP**.

Actions of Anterior Forearm Muscles

- **Pronator quadratus**—**Chief pronator** of forearm is the (initiates pronation and causes slow and sustained pronation) and is assisted by **pronator teres** (rapid and powerful pronation).
- **FCU** flexes and adducts the wrist
- **FCR** flexes and abducts the wrist
- **FDS**—flexion of middle and proximal phalanges
- **FDP**—ONLY muscles that causes flexion of **Distal Phalanges**.
- **FPL**—flexion of phalanges of thumb

Muscles of Posterior Compartment of Forearm

- These are the **extensor-supinator** muscles and are arranged in 2 layers:
- Superficial muscles
 - Anconeus
 - Brachioradialis
 - Extensor Carpi Radialis Longus (ECRL)
 - Extensor Carpi Radialis Brevis (ECRB)
 - Extensor digitorum
 - Extensor digiti minimi
 - Extensor Carpi Ulnaris
- Deep Muscles
 - Supinator
 - Abductor pollicis longus
 - Extensor pollicis longus
 - Extensor pollicis brevis
 - Extensor indicis

Note

- For origin and insertion of individual muscles please refer an anatomy textbook—however, the most important MCQ points about these are given below.

High Yield MCQ Points about Posterior Forearm muscles

- The **radial nerve** is responsible for extension of the elbow (triceps); wrist (Extensor carpi radialis) and fingers—hence called “**Great Extensor Nerve**”.
- All superficial and deep muscles of the posterior compartment (extensor muscles) are supplied by the deep branch of **radial nerve—posterior interosseous nerve (except brachioradialis, anconeus and ECRL, supplied directly by the radial nerve)**.
- **Anconeus** supplied by branch of radial nerve (nerve to anconeus, C7,8,T1) given off in the spiral groove of the arm.

- **Brachioradialis** is regarded as borderline muscle since developmentally it is an extensor muscle BUT functionally and topographically it is a flexor muscle.
- **Supinator jerk/reflex:** When the distal end of the radius is tapped there is a reflex flexion of the forearm. Positive response indicates the integrity of spinal segments **C7-C8**. It is the **brachioradialis that contracts** and NOT the supinator.

Actions of posterior forearm muscles

- ECRL and ECRB produce **extension** and **dorsiflexion** of the wrist.
- Extension of **metocarpophalangeal joints** is by extensor digitorum.
- Extension of **interphalangeal joints** is produced by **lumbricals and interossei**.
- **Supinator** causes slow and sustained supination with forearm extended; Rapid and forceful supination in flexed elbow is by biceps brachii.
- **Anconeus** is a weak extensor of the elbow and helps in **screwing movements**.

EXTRA EDGE

- **De Quervain’s tenosynovitis:** A condition where the synovial sheaths round the **abductor pollicis longus** and **extensor pollicis brevis** is inflamed. Pain and swelling occur in lateral part of the wrist.
- **Tennis elbow:** Inflammation of common extensor origin (especially **ECRB**) at lateral epicondyle of humerus—**Lateral epicondylitis**; seen in tennis players and violinists.
- **Golfer’s elbow:** **Medial epicondylitis**.
- **Mallet finger** or **Baseball finger:** Avulsion of insertion of **extensor digitorum** from base of distal phalanx—complete extension of phalanx is NOT possible and remains in a state of partial flexion.
- **Hammer thumb:** Spontaneous **rupture of EPL tendon** due to ischemia (injury to anterior interosseous artery as may occur in Colle’s fracture)—patient feels that the thumb has dropped as the interphalangeal joint of thumb cannot be extended.

Anatomical snuff box

- It lies between tendon of **extensor pollicis longus medially AND extensor pollicis brevis, abductor pollicis longus laterally**;
- It contains **radial artery**;
- Tenderness here, seen in **scaphoid #**;
- **Superficial branch of radial nerve** can be rolled against tendon of EPL.

HAND**Thenar and Hypothenar Muscles**

Thenar muscles	Nerve supply
Abductor pollicis brevis	Median N. (C8, T1)
Opponens pollicis	Median N. (C8, T1)
Flexor pollicis brevis	Superficial head by median N; Deep head by ulnar N.
Adductor pollicis	Deep branch of ulnar N. (C8, T1)
Abductor digiti minimi, Flexor digiti minimi brevis, Opponens digiti minimi	All by Deep branch of Ulnar N

Additional Points about Thenar and Hypothenar Muscles

- The **medial rotation** effected by **opponens pollicis** is helpful even when there is no complete opposition; it is required for **picking up objects**.
- The **flexor pollicis brevis** and **opponens pollicis** are in the same plane and usually appear to be a single sheet of muscle—this resembles the pronator teres both in direction of fibres and action and hence sometimes called "**pronator pollicis**".
- Tendon of insertion of **adductor pollicis** usually has a **sesamoid** bone. This muscle has **two heads of origin** which are separated by the radial artery.
- Abductor pollicis brevis** is the **first muscle** to show **weakness in carpal tunnel syndrome**.
- Remember that **flexor pollicis brevis** is a **composite muscle** since each head is supplied by a separate nerve.

Lumbricals

- Lumbricals** are 4 small muscles that arise from the tendons of **flexor digitorum profundus**.

- They are numbered from **lateral to medial side-I to IV**.
- I and II (lateral)** lumbricals supplied by median N., **III and IV (medial)** by deep branch of **ulnar N.**
- Lateral lumbricals** are **unipennate** and **medial** are **bipennate**.
- Lumbricals **flex the metacarpophalangeal joint** and **extend the interphalangeal joint—"writing position" or "Z movement"**.

Interossei

- Palmar interossei** are 4 unipennate muscles. Action—**AD**duction of fingers "**(PAD)**".
- Dorsal interossei** are 4 bipennate muscles. Action—**AB**duction of fingers "**(DAB)**".
- All the 8 interossei are supplied by deep branch of ulnar nerve

Palmaris Brevis

- Superficial fascia of palm** contains a **subcutaneous muscle, palmaris brevis** that improves the grip;
- Palmaris brevis supplied by **superficial branch of ulnar nerve**.
- Palmaris brevis is a subcutaneous muscle, (a layer of striated muscle that represents **panniculus carnosus**); other similar muscles are **platysma** in neck and **dartos** in scrotum.

EXTRA EDGE

- All the intrinsic muscles of the palm are supplied by deep branch of ulnar N. **except (LOAF)** – first and second Lumbricals, **O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis (superficial head).
- Since the **deep branch of ulnar nerve** supplies muscles involved in precision and fine movements of digits, it is called "**Musician's nerve**".
- Lumbricals** means "**earthworm**" in Latin.

NERVES OF THE UPPER LIMB**BRACHIAL PLEXUS****Formation of Brachial Plexus**

- It is formed by the anterior primary rami of spinal nerves **C5 to T1** with minor contributions from C4 and T2 roots.

- If **C4** also contributes to brachial plexus, it is called **pre-fixed plexus**; if **T2** also contributes it is called **post-fixed plexus**.
- C5 and C6** join to form **upper trunk**
- Root **C7** forms the **middle trunk**
- Root **C8 and T1** join to form **lower trunk**.
- Each trunk has anterior and posterior divisions.

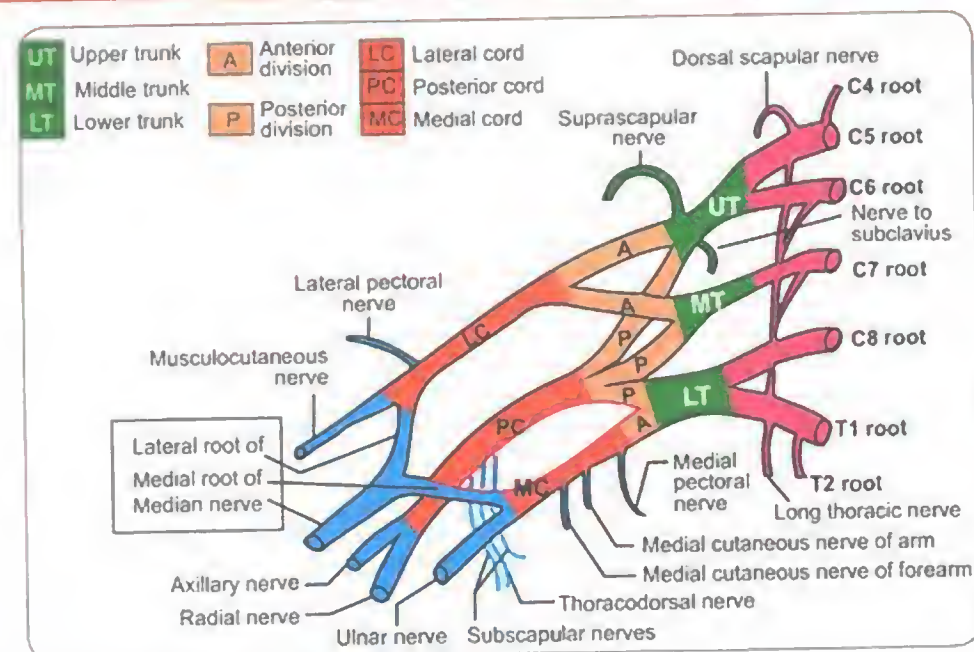


Fig. 2.25: Stages in the formation of brachial plexus

- Posterior division of all three trunks unite to form **posterior cord**.
- Anterior division of upper and middle trunk forms **lateral cord**. Anterior division of lower trunk forms **medial cord**.
- Mnemonic: **Roots - Trunks - Divisions - Cord - Branches**. ("Rash Truck Drivers Crash Badly!").

Branches of Roots

- Long thoracic N. of Bell** (C5, 6, 7) N. to **Serratus Anterior**, lesion leads to **Winging of Scapula**.
- Dorsal scapular N.** (C5)-supplies Rhomboids and Levator scapulae.

Branches of Trunk

- Only upper trunk gives branches. (**Middle and lower trunk has no branch**). The branches are
- Suprascapular N.** (C5, 6)-supplies Supraspinatus, Infraspinatus.
- N. to subclavius-supplies Subclavius.

Branches of Lateral Cord

- Lateral pectoral N.** (C5, 6, 7)—Clavicular head of Pectoralis Major.
- Musculocutaneous N.** (C5, 6, 7)—supplies **Coracobrachialis, Brachialis, Biceps**. Continues as **lateral cutaneous nerve of forearm** (supplies skin of lateral/

- radial border of forearm, i.e. it innervates a dermatome that does NOT lie superficial to its myotome!**).
- Lateral root of Median N.** (C5, 6, 7)

Branches of Medial Cord

- Medial pectoral N.** (C8, T1)-Sternal head of Pectoralis Major, Pectoralis minor.
- Medial cutaneous N. of arm** (C8, T1)
- Medial cutaneous N. of forearm.** (C8, T1)
- Medial root of Median N.** (C8, T1)
- Ulnar N.** (C7, 8, T1)

Branches of Posterior Cord

- Mnemonic: "**ULTRA**"
- Upper subscapular N.** (C5, 6) Subscapularis
- Lower subscapular N.** (C5, 6) **Teres Major**, a small part of subscapularis.
- Thoracodorsal N.** (C6, 7, 8) **Latissimus Dorsi**.
- Radial N.** (C5, 6, 7, 8, T1)-Extensors of forearm, wrist and hand
- Axillary or Circumflex N.** (C5, 6)

BRACHIAL PLEXUS INJURY**Erb-Duchenne Palsy**

- Follows **trauma during delivery** or **blow to shoulder**.
- Upper trunk** of brachial plexus (**C5, C6**) injury.

- **Erb's point** is the **meeting point of 6 nerves** ventral rami of C5 and C6; nerve to subclavius and suprascapular nerve; anterior and posterior division of upper trunk.
- **Waiter's/porter's/policeman's tip deformity** - Arm adducted and internally rotated, elbow extended and forearm pronated.
- **Muscles paralysed** are: deltoid, biceps brachii, brachialis, brachioradialis, supraspinatus, infraspinatus and supinator.
- Sensory changes are absent if C5 only is involved, BUT if C6 also involved, an **area of anaesthesia** is present over outer side of the arm.
- **Abduction and lateral rotation** of the arm (shoulder) are lost.
- When T1 is involved there may be a **ipsilateral Horner's syndrome** (sympathetic involvement).

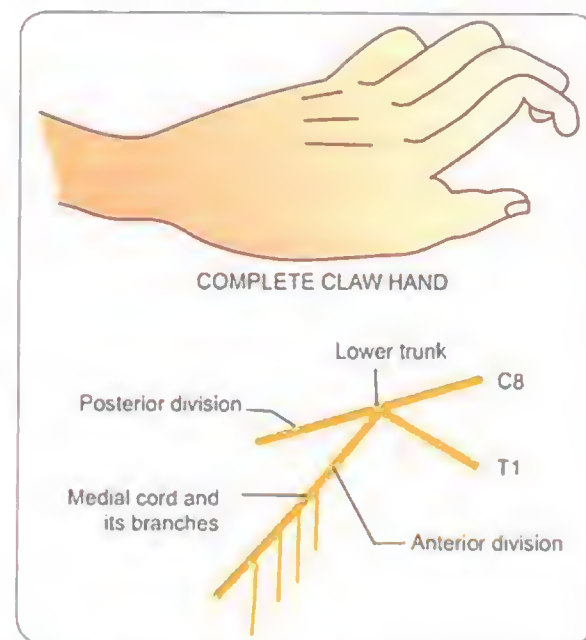


Fig. 2.27: Claw-hand deformity due to lesion of lower trunk of brachial plexus (Klumpke's palsy)

AXILLARY NERVE

- Axillary nerve (C5,6) is a.k.a **circumflex nerve**. It is a **mixed nerve** containing both **sensory and motor** fibres. It is a branch of **posterior cord** of brachial plexus.
- Branches:
- Trunk of axillary nerve gives an **articular twig** to shoulder joint and divides into anterior and posterior divisions.
- **Anterior** division supplies **deltoid**.
- **Posterior** division supplies **teres minor** which bears a **pseudoganglion**; continues as **upper lateral cutaneous nerve of arm** which supplies a part of skin over the insertion of the deltoid ('regimental badge' region)

Lesion of axillary nerve

- › Axillary nerve is liable to damage in **fracture surgical neck of humerus** and in **anterior dislocation of humeral head**.
- › Motor loss:
- › **Inability to abduct** the arm;
- › **Weakness of lateral rotation** of the arm;
- › **Loss of rounded contour** of the shoulder.
- › Sensory loss:
- › **"Regimental badge"** onesthesia.

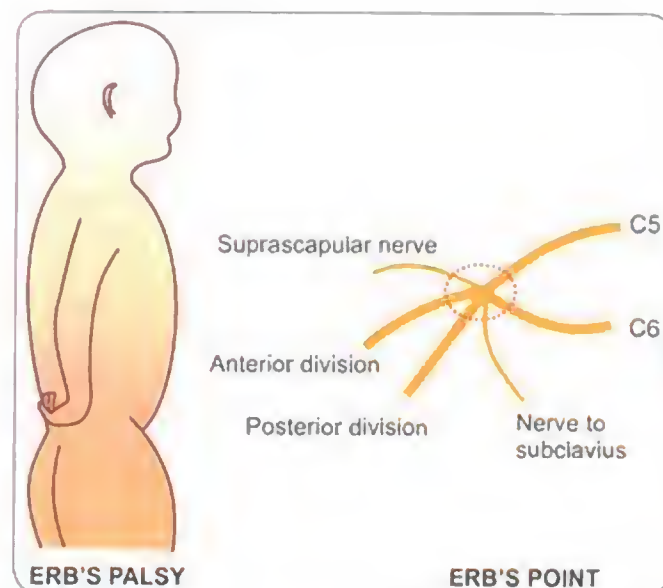


Fig. 2.26: Formation of Erb's point and typical waiter's tip position of upper limb in Erb's palsy due to lesion at Erb's point

- **Moro reflex and biceps jerk** are absent on the affected side; **ipsilateral diaphragmatic involvement** may be present.
- **Preganglionic lesions** have worse prognosis.

Klumpke's Paralysis

- **Forcible hyperabduction/hyperextension injury** (falling person trying to catch an object) or trauma during birth.
- **Lower trunk** of brachial plexus lesion (C8, T1)
- **Intrinsic hand muscle weakness** and **claw hand** may be seen.

MUSCULOCUTANEOUS NERVE

- Main nerve of the anterior compartment of the arm and a branch of **lateral cord** of brachial plexus.
- Root value: **C5,6,7**.
- It **pierces the coracobrachialis**.
- It **supplies** these muscles: **brachialis, coracobrachialis and biceps brachii**.

- It ends as the **lateral cutaneous nerve of the forearm** and supplies the **lateral half of front of forearm** and skin of **thenar eminence**.

Main Nerves

- Note: Radial, median and ulnar nerves are discussed in detail under Orthopedics chapter (Pg 715).

VESSELS OF THE UPPER LIMB

Axillary Artery

- Subclavian A. continues downward as the **Axillary A.** (**Axillary A.** begins at the outer border of First Rib and ends at the lower border of Teres Major. **Pectoralis minor** divides Axillary A. into three parts). Branches of each part are as in below table

1st part (1 branch)	Superior (Highest/supreme) Thoracic A.
2nd part (2 branches)	Thoraco-acromial A. Lateral Thoracic A.
3rd part (3 branches)	Subscapular A. (gives circumflex scapular A. and thoracodorsal A.) Anterior circumflex humeral A. Posterior circumflex humeral A.

Axillary Vein

- Axillary vein extends from the lower margin of teres major to the outer margin of first rib where it **continues as the subclavian vein**.
- It is formed by union of the **venae comitantes** of the brachial artery (brachial veins) and the basilic vein.
- **Cephalic vein** is its largest tributary.
- The axillary vein lies **medial to the axillary artery** throughout its course.
- The axillary vein is related on **medial side to medial cutaneous nerve of the arm** and on **lateral side to medial cutaneous nerve of forearm and ulnar nerve**.

Scapular anastomosis

- › Circumflex scapular branch of **subscapular A** (from third part of axillary A).

Scapular anastomosis

In case of block in subclavian or axillary artery, this anastomosis around scapula enlarges to a large extent to provide adequate blood supply to upper limb-may give rise to **'pulsating scapulo'**.

A communication between first part of subclavian artery and third part of axillary artery through anastomosis of following vessels.

- › **Suprascapular A** (a branch of thyrocervical trunk of first part of subclavian A)
- › Either **deep transverse cervical A** (a branch of thyrocervical trunk of first part of subclavian A) or the **dorsol scapular A** (branch of third part of subclavian A)

Brachial Artery

It begins at lower border of teres major as **continuation of axillary artery**. It terminates at the level of the neck of radius by dividing into **radial and ulnar arteries**.

Branches of Brachial Artery are:

- Profunda brachii A (**largest** branch)
- Superior, middle and inferior ulnar collateral arteries.
- Deltoid branch
- Muscular branches to arm muscles
- Nutrient artery to humerus

Branches of Profunda Brachii are:

- Nutrient A to humerus
- Muscular branches to adjacent muscles
- Middle collateral (posterior descending) branch: larger terminal branch
- Radial collateral (anterior descending) branch.

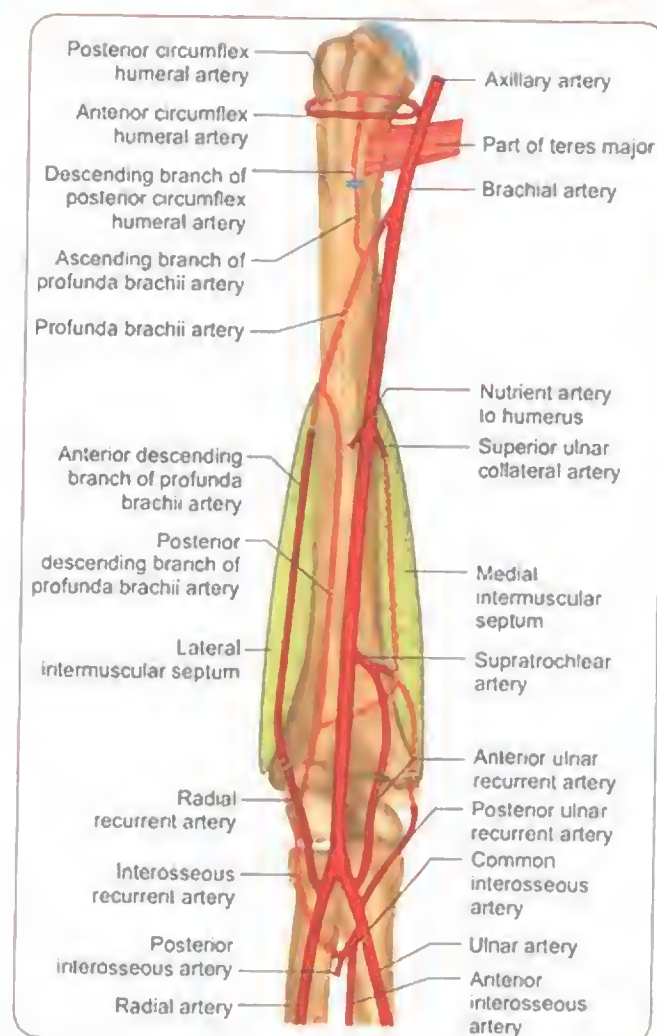


Fig. 2.28: Scheme to show the arteries of the arm and various anastomoses in the region

Ulnar Artery

- Begins as one of two terminal branches of the brachial artery and ends by dividing into deep palmar branch and **superficial palmar arch**
- Branches are:

- Anterior and Posterior ulnar recurrent artery
- Common interosseous artery that divides into anterior and posterior interosseous artery.
- Palmar carpal artery
- Dorsal carpal artery
- Deep palmar artery-joins the radial artery and completes the deep palmar arch.

Radial Artery

- Begins as the smaller terminal branch of brachial artery and ends in the palm by forming the **deep palmar arch**.
- Branches are:
 - Radial recurrent artery
 - Muscular branches
 - Palmar carpal artery
 - Dorsal carpal artery
 - Superficial palmar artery
 - Dorsal digital arteries of thumb and radial side of index finger
 - Princeps pollicis artery
 - Radialis indices artery

EXTRA EDGE

- Superficial palmar arch is mainly formed by the **Ulnar** artery
- Deep palmar arch is mainly formed by the **radial** artery.
- "**Carpal rete**": Anastomoses of the dorsal carpal branch of the ulnar and radial artery forms the **dorsal carpal arch** "carpal rete" (carpal network).
- Allen's test** is done to test the patency of the ulnar artery (done before radial artery is used for coronary graft since then, ONLY ulnar artery shall supply the palm).

Arteries for Cannulation

- Common arteries used for **cannulation** are **radial artery** (just above wrist) and **posterior tibial artery** (above medial malleolus).
- Arteries **NOT** suitable for cannulation due to poor collateral circulation:
 - Ulnar artery: (also since very close to ulnar nerve)
 - Brachial artery (also since very close to median nerve)
 - Dorsalis pedis artery

OTHER IMPORTANT REGIONS OF UPPER LIMB

PECTORAL REGION

Sternal Angle

- Sternal angle of Louis** is palpable as transverse ridge and indicates the position of the **second costal cartilage** and indicates the position of the second rib from which the other ribs are counted downwards.

- Cutaneous nerves on the anterior chest wall above the sternal angle are derived from cervical plexus and below that level are derived from intercostal nerves. At the level of sternal angle C4 dermatome meets T2 dermatome. This interruption in the sequential order of dermatomes is due to the fact that **C5 to T1 dermatomes are dragged into the upper limb bud** during embryonic life.

Clavipectoral Fascia

- The clavipectoral fascia (CPF) **extends from the axillary fascia to enclose the pectoralis minor and subclavius muscles** and attaches to the clavicle.
- The part of CPF superior to pectoralis minor is the **costocoracoid membrane** and the part inferior to it is the **axillary ligament of the axilla**.

Structures piercing the clavipectoral fascia

- Cephalic vein
- Acromio-thoracic artery
- Lateral pectoral nerve;
- Lymphatic vessels
- ("CALL")

Muscles of the Pectoral Region

Origin	Insertion	Actions	Nerve supply
Pectoralis major			
By two heads Clavicular head: medial half of anterior surface of clavicle Sternocostal head: costal cartilages, 1st to 10th, body of sternum and second to sixth costal cartilages. Aponeurosis of external oblique muscle.	Lateral lip of intertubercular sulcus of humerus by a U shaped bilaminar tendon.	Adduction and medial rotation of the arm. Flexion of the arm. Extension of flexed arm. When the arm is raised above the head and fixed, the muscle can raise the thorax (as in climbing) (helped by latissimus dorsi) Helps in forced inspiration	Lateral pectoral nerve (C5, C6, C7) and Medial pectoral nerve (C8, T1)
Pectoralis minor			
1st, 4th and 5th ribs adjacent to costal cartilages	Into the medial margin and upper surface of coracoid process of scapula	Protraction of scapula (along with serratus anterior) Depression of scapula (with lower fibres of trapezius)	Medial Pectoral nerve (C8, T1); lateral pectoral nerve may also supply this muscle
Subclavius			
Junction of first rib and costal cartilage	A groove on middle third of inferior surface of the clavicle	Steadies the clavicle during movements of the scapula	Nerve to subclavius (C5, C6), (branch of upper trunk of brachial plexus)

EXTRA EDGE

- Anterior axillary fold** is produced by the **pectoralis major**
- Pectoralis major** is the MC muscle to be congenitally absent (**Poland syndrome**).
- Pectoralis minor** divides axillary artery into 3 parts.
- Pectoralis minor** is a key surgical landmark for identifying axillary lymph nodes during surgical dissection of the axilla.
 - Level I nodes (anterior, posterior and lateral groups) are located below and lateral to the lower margin of the muscle.
 - Level II nodes (central group) are located behind and the interpectoral or Rotter's nodes in front of the muscle.
 - Level III (apical group) lie above the upper margin of the muscle.

AXILLA

- Axilla is pyramidal in shape and has an apex, base and 4 walls.
- Anterior axillary fold** is formed by the **pectoralis major**.
- Posterior axillary fold** is formed by the **teres major and latissimus dorsi**.
- Axillary abscess** is drained by **incision in the base** of the axilla.
- Contents of the axilla**
 - Axillary artery and vein
 - Cords of brachial plexus and their branches
 - Axillary sheath** (prolongation of **prevertebral layer** of deep cervical fascia) around axillary artery and cords of brachial plexus.

- Long thoracic nerve
- Intercostobrachial nerve
- Axillary lymph nodes
- Axillary tail of Spence
- Axillary fat

Axillary Lymph Nodes

- Axillary lymph nodes drain lymph from
 - Most of the mammary gland
 - Entire upper limb
 - Thoracoabdominal walls upto the level of umbilicus in front and upto level of iliac crest on the back
- The lymph nodes are classified into 5 groups
 - **Lateral (brachial)** group, along the axillary vein;
 - **Anterior (pectoral)** group, along the lateral thoracic vessels;
 - **Posterior (subscapular)** group, along the subscapular vessels;
 - **Central** group, embedded in fat in the centre of the axilla;
 - **Apical** group, which lie above the level of the pectoralis minor tendon in continuity with the lateral nodes and which receive the efferents of all the other groups
 - **Interpectoral** group (**Rotter's nodes**), a few nodes lying between the pectoralis major and minor muscles.

MAMMARY GLAND (BREAST)

- Mammary gland is a **modified sweat gland** and extends from the **2nd to 6th ribs** in the midclavicular line.
- **Axillary tail (of Spence)** of the breast pierces the deep fascia (through foramen of Langer) and comes to lie in the axilla.
- The **lobule** is the basic structural unit of the mammary gland. From 10 to over 100 lobules empty via ductules into a **lactiferous duct**, of which there are 15-20. Each lactiferous duct is lined with a spiral arrangement of contractile myoepithelial cells and is provided with a terminal ampulla, a reservoir for milk or abnormal discharges
- The fibrous stroma of the breast forms septa called the **suspensory ligaments of Cooper** that anchor the skin and gland to the pectoral fascia. These ligaments account for the dimpling of the skin overlying a carcinoma.
- 75% of breast lymphatics drain to the **axillary nodes** and 20% to **internal mammary** nodes and 5% to the posterolateral intercostal nodes. Lymphatic plexus just beneath areola is the **subareolar plexus of Sappey**.
- The breast is a compound **tubuloalveolar gland**; according to its mode of secretion it is classified as both **merocrine** and **apocrine** gland.

- The **nipple** is mainly innervated by **4th intercostal nerve**.
- **Circulus venosus of Haller**: anastomotic circle of veins around base of the nipple

Blood Supply of the Breast

- Perforating branches of **Internal mammary artery** in the II, III and IV intercostal spaces.
- Thoracoacromial, lateral thoracic and superior thoracic branches of axillary artery
- Mammary branches from 2nd, 3rd and 4th posterior intercostal arteries.

Congenital breast anomalies

- **Athelia** = Absence of the nipple, areola
- **Polythelia** = Supernumerary nipple and areola
- **Amastia** = Complete absence of breast development
- **Polymastia** = Supernumerary (accessory) breasts
- **Amazia** = Nipple is present BUT glandular tissue absent

CUBITAL FOSSA

- **Boundaries:**
 - Medially-**pronator teres**
 - Laterally-**brachioradialis**
 - Superior-**interepicondylar line of humerus**
- **Contents (medial to lateral side):**
 - **Median N (medial most)**
 - **Brachial Artery** (between median N and biceps)
 - **Biceps brachii Tendon** (midline structure)
 - **Radial N (lateral most under cover of brachioradialis)**
- Mnemonic: "**My Best Buddy Ramgopal!**"

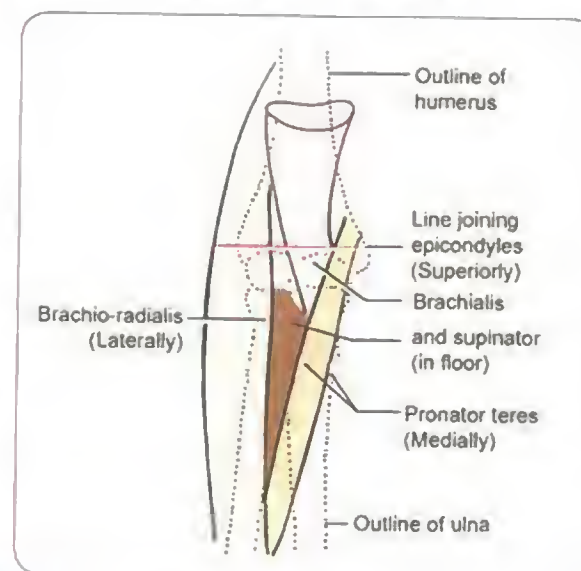


Fig. 2.29: Boundaries of the cubital fossa

EXTRA EDGE

- The deep fascia of the roof of cubital fossa is strengthened by the bicipital aponeurosis which is crossed superficially by the median cubital vein. This aponeurosis provides a firm platform to steady this vein during venipuncture and protects the underlying brachial artery and median nerve. Hence bicipital aponeurosis was also called **grace Deix tendon (tendon of divine grace)**!

SPACES OF THE HAND

- **Thenar space**: closely related to **radial bursa**.
- **Midpalmar space**: closely related to **ulnar bursa**.

LOWER LIMB

BONES AND JOINTS OF LOWER LIMB

HIP BONE

- Also called as **innominate** bone (since it doesn't conform to any regular shape!); **coxal bone**.
- Parts of hip bone are **ilium**, **pubis** and **ischium**.
- **Anterior superior iliac spine** (ASIS) passing through upper border of **S1** (sacral promontory)
- **Tubercle of iliac crest** lies at upper border of **L5-transstubercular** plane passes through upper border of L5
- **Supracristal plane** passes through **highest point of iliac crest (at L4 level)**—this plane determines the site of **lumbar puncture**.
- **Posterior superior iliac spine** is at S2 level
- **Posterior inferior iliac spine** is at S3 level.

Attachments to Iliac Crest

- Iliac crest is divisible into **ventral segment (anterior 2/3)** and **dorsal segment (posterior 1/3)**.
- Ventral segment has **outer lip**, **intermediate area** and **inner lip**.
- Dorsal segment has **lateral (outer) slope** and **medial (inner) slope**.
- Muscles attached to **outer lip of ventral segment**
 - Origin of **tensor fascia lata** in front of iliac tubercle
 - Insertion of **external oblique** in anterior 2/3
 - Origin of **latissimus dorsi** in its posterior 1/3
- Intermediate area gives origin to internal oblique
- Muscles attached to inner lip of ventral segment
 - Origin of **transversus abdominis** in anterior 2/3

- Origin of **quadratus lumborum** in posterior 1/3

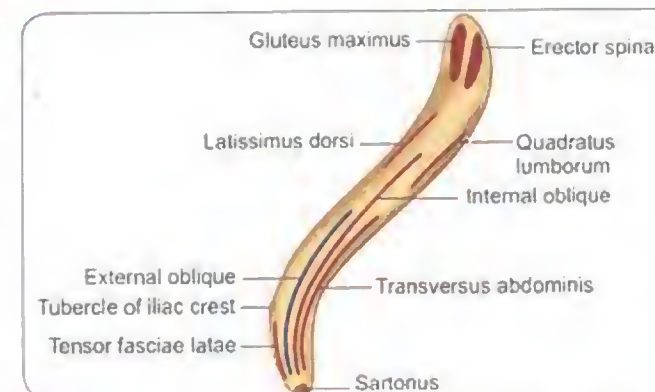


Fig. 2.30: Scheme to show the attachments on the right iliac crest

- Muscle taking origin from dorsal segment:
 - **Erector Spinae** from **Medial** slope
 - **Gluteus Maximus** from **Lateral** slope
 - Mnemonic: "**Every Sunday My Good Morning is Late**".
- ASIS gives origin to sartorius and attachment to inguinal ligament.
- Friends, just read the above text and see the below figure to remember the attachments easily.

Attachments to Ischial Tuberosity

- Superolateral area: origin of **semitendinosus**
- Inferomedial area: origin of **semitendinosus** and **long head of biceps femoris**
- Outer lower area: origin of **adductor magnus**.

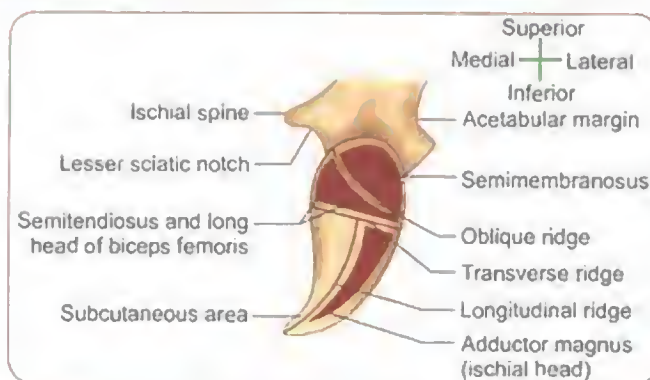


Fig. 2.31: Attachments of ischial tuberosity

EXTRA EDGE

- **Posterior superior iliac spine** lies below the skin dimple called **dimple of Venus** (prominent in females) in upper part of gluteal region. It corresponds to **spine of S2**. This site is used to draw **bone marrow for biopsy**.

Greater Sciatic Notch

- Greater sciatic notch is converted into **greater sciatic foramen** with the help of sacrotuberous and **sacrospinous ligaments**
- Greater sciatic foramen gives passage to the **piriformis**, seven nerves (branches of sacral plexus) and three blood vessels
- Structures passing above piriformis:
 - Superior gluteal nerve and vessels
- Structures passing below piriformis (Mnemonic: "**PIN, PINS!**"):
 - Posterior cutaneous nerve of thigh
 - Inferior gluteal nerve and vessels
 - Nerve to quadratus femoris
 - Pudendal nerve
 - Internal pudendal vessels
 - Nerve to obturator internus
 - Sciatic nerve

EXTRA EDGE

- Since structures which go to gluteal region from pelvis, do so through the greater sciatic foramen-hence it is called "**doorway to the back**".
- In **piriformis syndrome**, **sciatic nerve** is compressed due to hypertrophy or spasms of piriformis muscle at the greater sciatic foramen.

Lesser Sciatic Notch

- Lesser sciatic notch is converted into **lesser sciatic foramen** by **sacrospinous and sacrotuberous ligaments**.

- **Superior and Inferior gemelli** arise from the respective margins of the notch.
- Structures passing through lesser sciatic foramen (mnemonic: "**PINTO!**"):
 - Pudendal nerve
 - Internal pudendal vessels
 - Nerve to obturator internus
 - Tendon of Obturator Internus

FEMUR

- The **femur** is the longest and **strongest** bone.
- The femur has **shaft** and **lower end** (medial and lateral epicondyle).

Upper End of Femur

- Upper end has **head, neck, greater trochanter and lesser trochanter**.
- Head is more than half a sphere; it has a depression called **fovea capitis** paracentrally to which **ligamentum teres** is attached.
- Neck connects head to shaft and normal neck shaft angle (angle of inclination) is **125 degrees**. (at birth it is **150 degrees**).
- In **coxa vara** the angle is decreased and in **coxa valga** it is increased.
- Muscular **Insertions on greater trochanter** are:
 - **Piriformis** at apex
 - **Gluteus medius** on lateral surface
 - **Gluteus minimus** on anterior surface
 - Medial surface upper part-insertion of **obturator internus with 2 gemelli**
 - Medial surface lower part-trochanteric fossa for insertion of **obturator externus**.
- **Lesser trochanter** gives insertion to **ilopsoas tendon**.
- **Intertrochanteric line** marks the junction of neck and shaft **anteriorly**. It gives attachment to **capsule of hip joint**
- **Intertrochanteric crest** connects the two trochanters **posteriorly**. It shows a **quadratus tubercle** to which the **quadratus femoris** is inserted.

Shaft of Femur

- It has **forward convexity** and has a **thickened ridge** on **posterior aspect** of middle 1/3 called **linea aspera**.
- The linea aspera has medial and lateral lips which diverge upwards; medial lip becomes continuous with **spiral line**; lateral lip becomes continuous with **gluteal tuberosity**. Deep fibres of **gluteus maximus** are inserted into gluteal tuberosity.

- Attachments on posterior aspect of shaft are from lateral to medial side- "**I Like Boys-My Boyfriend Loves Me!**" (7 muscles and 3 septa).
 - Vastus **I**ntermedius
 - Vastus **L**ateralis (lateral lip of linea aspera)
 - Lateral intermuscular septum
 - Short head of **B**iceps femoris
 - Posterior intermuscular septum
 - Adductor **M**agnus
 - Adductor **B**revis
 - Adductor **L**ongus
 - Medial intermuscular septum
 - Vastus **M**edialis (medial lip of linea aspera)

Lower End of Femur

- **Medial epicondyle-tibial collateral ligament** is attached to it.
- Above and behind the medial epicondyle is the **adductor tubercle**-a palpable landmark; the **lower epiphyseal line** passes through adductor tubercle.
- **Lateral epicondyle-fibular collateral ligament** is attached to it.
- Anterior cruciate ligament is attached to inner surface of **Lateral condyle** and **Posterior cruciate ligament** to inner surface of **Medial condyle**. ("**Always Love Practicing Medicine!**")



Fig. 2.32: Parts and attachments of femur in anterior view

Blood Supply of Femoral Head

- **Medial circumflex femoral artery**-major blood supplier to femoral head through following branches:
 - **Lateral (superior) retinacular artery**; a.k.a **lateral ascending cervical artery**-main artery
 - Medial (inferior) and posterior retinacular arteries.
- **Lateral circumflex femoral artery**-gives anterior retinacular artery
- **Obturator artery**-gives artery of ligamentum teres.

Ossification

- Femur is **second** long bone in body to ossify (after clavicle).
- Shaft and neck develop from one primary centre.
- Upper end (greater, lesser trochanters and head) ossify from 3 secondary centers.
- **Lower end** ossifies from **one secondary center**-appears at **9th month** of fetal life-its presence is **proof of viability of the fetus**-medicolegal importance.

EXTRA EDGE

- The **lower end of femur** is **growing end**; nutrient artery is directed upwards.
- **Nutrient artery** is a branch of **second perforating artery** which is in turn a branch of **profunda femoris artery**.

TIBIA

- Tibia is **second longest bone** in the body (after femur).
- It has broad upper end, shaft and narrow lower end.

Upper End of Tibia

- Upper end of tibia has **medial and lateral condyles and intercondylar area**.
- Superior surface of **medial condyle** articulates with medial condyle of femur and medial meniscus. Its posterior surface presents deep groove for insertion of **semimembranosus**.
- Superior surface of **lateral condyle** articulates with lateral condyle of femur and lateral meniscus.
- Inferolateral surface of lateral condyle articulates with head of fibula at the superior tibiofibular joint.
- Anterior surface of lateral condyle presents a facet (**Gerdy's tubercle**) for attachment of **iliotibial tract**.
- **Tibial tuberosity-ligamentum patellae** is attached to the upper smooth part and subcutaneous **infrapatellar bursa** to lower rough part.
- **Intercondylar area**: structures attached are (anterior to posterior):

- Anterior horn of **M**edial meniscus
- Anterior cruciate ligament
- Anterior horn of **L**ateral meniscus
- Posterior horn of **L**ateral meniscus
- Posterior horn of **M**edial meniscus
- Posterior cruciate ligament.
- Mnemonic: "**MALL-MP**"

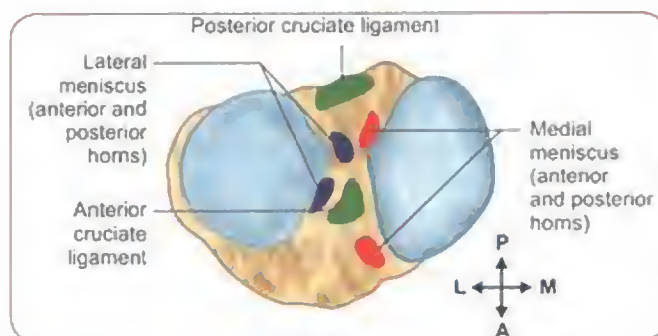


Fig. 2.33: Structures attached to intercondylar area of tibia

Shaft of Tibia

- **Anterior border of tibia** is the "**shin**"-entirely subcutaneous-hence majority of tibial fractures are of open type.
- **Lateral border** is also called **interosseous border** since it gives attachment to interosseous membrane.
- **Medial surface**, in its **upper end** receives insertions of **Sartorius, Gracilis and Semitendinosus** from before backwards ("Girl between two Surgeons"). The pattern of insertion of these 3 muscles in the shape of the 'foot of a goose'-"**pes anserinus**"-hence these muscles are called **anserine muscles** and the bursa between them and the **tibial collateral ligament** is called **anserine bursa**.
- **Lateral surface**: upper 2/3 gives origin to **tibialis anterior muscle**.
- **Posterior surface**: has a thickened ridge called "**soleal line**".



Fig. 2.34: Attachments of tibia and fibula as seen from anterior aspect

Lower End of Tibia

- **Medial malleolus** is grooved by tendon of **tibialis posterior**. The apex of medial malleolus gives attachment to **deltoid ligament** of ankle joint.

Blood Supply of Tibia

- Nutrient artery is derived from posterior tibial artery-it is the largest nutrient artery in the body; it is directed inferiorly (upper end is growing end).

EXTRA EDGE

- **Long saphenous vein** (accompanied by saphenous nerve) crosses the lower third of the medial surface; it is often cannulated in front of medial malleolus.

FIBULA

- Lateral surface of **neck of fibula** is closely related to **common peroneal nerve**.
- **Styloid process** on neck of fibula gives attachment to **fibular collateral ligament** of knee joint and to **biceps femoris**.
- **Nutrient artery to fibula** is from the **peroneal artery**.

EXTRA EDGE

- By **law of ossification**, the secondary centre that appears first is the last to fuse and the one to appear last is the first to fuse. All long bones **except fibula** abide by this law.
- **Fibula** is the ideal bone for taking pieces for **bone grafting**.

TARSAL BONES

- There are 7 tarsal bones:
 - Proximal row: calcaneus below and talus above it.
 - Distal row: Cuneiforms (medial, intermediate and lateral) and cuboid
 - **Navicular** bone: is interposed between proximal and distal row. It resembles a **small ship**.
- **Talus** is shaped like a **tortoise**.
- The **talus** has **NO** muscular attachments.
- **Calcaneus** is the **heel bone**.
- **Calcaneus** is the largest **tarsal** bone

METATARSAL BONES

- The **first** metatarsal is **shortest and thickest**
- **Second** metatarsal is **longest and least mobile**.
- **Third** metatarsal has a **styloid process**.
- **Tuberosity of fifth** metatarsal receives insertion of **peroneus brevis**.

Accessory Bones in Skeleton of Foot

- **Os trigonum**: separate ossification tendon for **lateral tubercle of talus**.
- **Os vesalius**: tuberosity of **fifth metatarsal** ossifies from separate center
- **Os naviculare secundarium**: **accessory navicular bone** is an extra navicular bone seen from birth.

HIP JOINT

- **Multi-axial, ball and socket type of synovial joint**.

Ligaments of Hip Joint

- Intracapsular ligaments
 - **Acetabular labrum**: depends the acetabulum and is deficient inferiorly.
 - **Transverse acetabular ligament**: is a continuation of acetabular labrum across the acetabular notch.
 - **Ligament of head of femur (ligamentum teres or round ligament)**: it connects the transverse acetabular ligament to fovea of head of femur.
- **Fibrous capsule**:
 - Medially: attached to margins of acetabulum, labrum.
 - Laterally: anteriorly it is attached to **intertrochanteric line** on **anterior aspect** and to **intertrochanteric crest** on **posterior aspect** of the neck of femur. Thus entire anterior surface of neck is intracapsular and posterior surface of neck is partly intracapsular.
- **Ileofemoral ligament of Bigelow**:
 - It is the **strongest ligament** of the body; It is **inverted-Y shaped**
 - The **stem of the Y** is attached superiorly to the **anterior superior iliac spine**
 - Inferiorly attached to the **intertrochanteric line** of femur
 - Ileofemoral ligament prevents the natural tendency of the body to fall backward (**prevents overextension** of hip joint).
- Pubofemoral ligament
- Ischiofemoral ligament

Stabilisers of Hip Joint

Static stabilisers	Dynamic stabilisers
Joint capsule Ligaments (ileofemoral, pubofemoral, ischiofemoral) Labrum	Muscles acting across the joint Iliopsoas; hip abductors; short external rotators

Nerve Supply

- **Femoral nerve** via branch to rectus femoris
- Nerve to quadratus femoris
- Anterior division of obturator nerve
- Superior gluteal nerve

Movements at Hip Joint

Movement	Main muscle	Accessory muscle
Flexion	Iliopsoas	Pectineus, sartorius, rectus femoris
Extension	Gluteus maximus	Hamstring muscles
Adduction	Adductors-longus, brevis and magnus	Pectineus and gracilis
Abduction	Gluteus medius and minimus	Tensor fascia lata and minimus
Medial rotation	Gluteus medius and minimus	Tensor fascia lata and adductor muscles
Lateral rotation	Obturator externus and internus, gemelli, quadratus femoris	Piriformis, gluteus maximus, sartorius
Circumduction	Sequential contraction of all muscles responsible for above movements	

Trendelenburg's sign

- When the body weight is supported on one limb, the tendency of the unsupported side to sag down is counteracted by **gluteus medius** and **minimus** (i.e. the **abductor mechanism**) of the supported (opposite) side.
- In conditions given below, the **abductor mechanism is defective** and the unsupported side of pelvis drops. This is **positive Trendelenburg's sign/Trendelenburg's gait/Gluteus medius gait**. It is seen in
 - Paralysis of the gluteus medius, minimus.
 - Congenital dislocation of hip joint,
 - Ununited fracture neck of femur
 - Coxa vara,

KNEE JOINT

- **Largest joint** in the body; **coudylar** type of **compound synovial** joint.
- It consists of **femoro-tibial** and **femoro-patellar** articulations.

Stabilisers of Knee Joint

Static stabilisers	Dynamic stabilisers
<ul style="list-style-type: none"> • Joint capsule • Meniscus • Cruciate and collateral ligaments 	Muscles acting across the joint <ul style="list-style-type: none"> • Quadriceps and hamstring muscles

Fibrous Capsule of Knee Joint

- It is **deficient in anterior part of joint** where it is replaced by quadriceps femoris tendon, patella and ligamentum patellae.
- There are two openings in the capsule
 - For tendon of popliteus-thus **popliteus tendon** is **intracapsular**.
 - **For Suprapatellar bursa** that **always communicates** with knee joint cavity.

Ligaments of Knee Joint

- **Ligamentum patellae** is **not** a ligament, it is the central portion of common **tendon of quadriceps femoris**.
- **Oblique popliteal ligament**
 - It is an expansion from tendon of **semimembranosus** that strengthens the capsule posteriorly.
 - **Popliteal artery** is in close contact with this ligament.
 - It is **pierced by** (1) **middle genicular artery** (2) **middle genicular nerve** and (3) genicular branch of posterior division of **obturator nerve**.
- **Arcuate popliteal ligament**.
- **Tibial (medial) collateral ligament:**
 - Superiorly it is attached to **medial epicondyle** of femur just below adductor tubercle.
 - Inferiorly it divides into superficial and deep parts
 - **Superficial part** is attached to medial surface of tibia between the medial margin of tibia and the insertions of sartorius, gracilis and semitendinosus. It covers the **inferior genicular nerve and vessels**.
 - **Deep layer** is fused with the **capsule** and peripheral **margin of medial meniscus**
 - Morphologically, it represents the degenerated tendon of the **adductor magnus**.
- **Fibular (lateral) collateral ligament:**
 - It is rounded, cord like and short
 - Morphologically, it represents degenerated tendon of **peroneus longus**

Cruciate ligaments

- They are named anterior and posterior **depending on their attachment to the tibia**.
- They are **intracapsular but extrasynovial** (i.e. they are located within the boundary described by the articular capsule, BUT they are NOT within the synovial membrane and thus not bathed in synovial fluid!)
- They are supplied by **middle genicular artery**.
- They give **antero-posterior stability** to knee.
- **Anterior Cruciate Ligament (ACL)**
 - It **prevents posterior dislocation of femur on tibia** and **anterior dislocation of tibia on femur**. It becomes **taut in extension** along with all other ligaments.
- **Posterior cruciate ligament (PCL)**
 - It prevents anterior dislocation of femur on tibia and posterior dislocation of tibia on femur. It becomes **taut during flexion** with anterior cruciate ligament.
- **Meniscus** (**semilunar** cartilages)
- They are **cresecent shaped fibrocartilage** placed on articular surface of tibia.
- They help to make the articular surfaces more congruent, also serve as **shock absorbers**.
- The **medial meniscus** is **more commonly damaged** than lateral, because of its **fixity** to the tibial collateral ligament.
- Ligaments related to menisci are coronary ligament, meniscofemoral ligament and transverse ligament.
- **Coronary ligament** attaches the periphery of menisci to the periphery of **tibial condyles**.
- **Menisco-femoral** ligaments extend from posterior part of the lateral meniscus and end on the femoral medial condyle in a/w **posterior cruciate ligament**.
 - **Anterior** menisco-femoral ligament is ligament of **Humphrey**;
 - **Posterior** menisco-femoral ligament is Ligament of **Wrisberg**.

Locking and Unlocking of Knee

- **Locking of knee** occurs **due to medial rotation of femur on fixed tibia** during the last stage of extension.
- Locking is caused by **quadriceps femoris**.
- Locking allows the knee to maintain the position of full extension (as in standing for hours together) without much strain on the quadriceps.
- **Unlocking** is defined as **lateral rotation of femur on tibia** at the **beginning of flexion** of locked knee.
- **Unlocking muscle** is **Popliteus**-hence also called "**key of the knee joint**".

Movements of Knee Joint

Movement	Main muscle	Accessory muscle
Flexion	Hamstring muscles (biceps femoris, semi-tendinosus and semi-membranosus)	Popliteus, gracilis, sartorius and plantaris
Extension	Quadriceps femoris	Tensor fascia lata, iliotibial tract
Medial rotation (of flexed leg)	Popliteus, semi-membranosus and semi-tendinosus	
Lateral rotation (of flexed leg)	Biceps femoris	

ANKLE JOINT

- A.k.a talocrural joint; a synovial joint of hinge variety; bones articulating are tibia, fibula and talus.

Deltoid Ligament (Medial Ligament)

- Attached above to the **tip of medial malleolus**; it consists of superficial and deep parts
- Superficial part has 3 bands
 - **Tibionavicular** part: attached to navicular tuberosity and spring ligament
 - **Tibiocalcaneal** part: attached to sustentaculum tali of calcaneum
 - **Posterior tibiotalar** part: attached to medial tubercle and medial surface of talus.
- Deep part attaches to the talus to form **anterior tibiotalar ligament**.

Lateral Ligament of Ankle Joint

- This consists of 3 discrete parts:
 - Anterior talofibular (**weakest ligament** of ankle),
 - Posterior talofibular and
 - Calcaneofibular ligament.

Relations of Ankle Joint

- Anteriorly (from **medial to lateral side**): Tibialis anterior, Extensor Hallucis longus, Anterior tibial artery, deep peroneal Nerve, Extensor Digitorum longus and peroneus Tertius.
- Mnemonic: "**Tendulkar Had A Nice Day Today!**".
- Posteriorly (from **medial to lateral side**): Tibialis posterior; flexor Digitorum longus; Posterior tibial Artery; Posterior tibial Nerve; Flexor Hallucis Longus
- Mnemonic: "**The Doctors Are Not Here!**".

Movements at Ankle Joint

Plantarflexion (Least stable position)	Main muscle: Gastrocnemius, soleus Accessory muscles: plantaris, tibialis posterior, flexor digitorum longus and flexor hallucis longus
Dorsiflexion (Most stable position)	Main muscle: Tibialis anterior Accessory muscles: Extensor hallucis longus, extensor digitorum longus and peroneus tertius.

EXTRA EDGE

- **Anterior talofibular** is the **most commonly injured ligament** around the ankle; **posterior talofibular** is the **least commonly injured**.
- When weight bearing, the **ankle is most stable in the dorsiflexed** position—as the wider (anterior) part of the **wedge-shaped talus** is lodged in the space between the fibula and tibia.

INTERTARSAL JOINTS

- **Subtalar Joint**
 - **Plane type** of synovial joint;
 - **Posterior talocalcaneal joint** is often called subtalar joint.
- **Talocalcaneonavicular joint:**
 - Roughly a **ball and socket** type of synovial joint.
- **Calcaneocuboid joint:**
 - **Saddle joint**

- Three ligaments are **bifurcated** ligament, **long plantar** ligament and **short plantar** ligament.
- **Transverse Tarsal (midtarsal) Joint** –
 - It includes **talocalcaneonavicular joint** (**ball and socket type**) and **calcaneocuboid** (**saddle**) joint.
- **Movements** at the intertarsal joint are
 - **Inversion:** Tibialis anterior and posterior;
 - **Eversion:** Peroneus longus and brevis
- When the calcaneus is in eversion (In the **pronated foot**) the **talonavicular** axis and **calcaneocuboid** axis are parallel.

ARCHES OF FOOT

- **Medial longitudinal arch (MLA):**
 - **Bones of the MLA** are calcaneus, talus, navicular, cuneiform and medial three metatarsal bones including the two metatarsal bones under the head of first metatarsal bone.
 - **Head of talus** is the '**keystone**' of MLA.
 - Supports of the medial arch:
 - **Spring ligament** (**plantar calcaneonavicular ligament**)-critical ligament
 - **Plantar aponeurosis;** abductor hallucis and flexor digitorum brevis; **tibialis anterior;** tibialis posterior; **flexor hallucis longus.**
 - **Pes planus:** due to collapse of MLA
- **Lateral longitudinal arch:** the long plantar and short plantar ligaments are the main ligamentous supports.
- **Anterior transverse arch** is a **complete arch**.

MUSCLES OF LOWER LIMB

MUSCLES OF GLUTEAL REGION

1. Gluteus maximus, medius, minimus.
2. Obturator internus,
3. Gemelli (superior and inferior),
4. Quadratus femoris
5. Piriformis.

Gluteus maximus	Gluteus medius and minimus
<ul style="list-style-type: none"> • Inserted into gluteal tuberosity, iliotibial tract • Chief extensor of the thigh at the hip joint. • Helps in rising from sitting position. • Maximus supplied by Inferior Gluteal Nerve (L5, S1, S2). ("MAXIGN"-magazine!) 	<ul style="list-style-type: none"> • Inserted into greater trochanter of femur • These are powerful abductors of the thigh. • Supplied by the superior gluteal nerve (L4, L5, S1).

Other Important Points about Gluteal Region Muscles

- In adults, the **upper outer quadrant of the gluteus maximus** is the most frequently used site for **IM injection**.
- Injury to the **superior gluteal nerve** can result in a **Trendelenburg gait** (gluteus medius gait)-discussed under hip joint.
- Gemelli **superior** supplied by: Nerve to **obturator internus**.
- Though the **inferior gemellus** gets a separate innervation from **nerve to quadratus femoris**, it is better to consider the obturator internus and two gemelli as a single unit-these 3 muscles cannot have a separate action and hence are called "**triceps coxae**".
- Short **lateral rotators** of thigh (they are lateral rotators of thigh BUT their main function is to act as ligaments which retain the head of femur in acetabulum:

- Piriformis,
- Obturator internus with gemelli
- Obturator externus
- Quadratus femoris

ANTERIOR THIGH MUSCLES

1. Tensor fascia lata
2. Sartorius
3. Quadriceps femoris (rectus femoris, vastus-lateralis, medialis and intermedius).

Other Important Points about Anterior Thigh Muscles

- **Sartorius** flexes, abducts and laterally rotates the thigh and flexes the knee.
- Sartorius is **longest muscle** in the body-also called **tailor's muscle**.
- All cause **extension of knee** (except sartorius, which causes flexion).
- All are supplied by **femoral N. (L2, 3, 4)**; sartorius by anterior division and rest by posterior division
- Vastus **medialis** stabilises the **patella**.
- **Tensor fascia lata** shares its **insertion with the gluteus maximus** (iliotibial tract) but shares its **nerve supply with gluteus medius and minimus** (superior gluteal nerve).

MEDIAL THIGH MUSCLES

These muscle of medial (adductor) compartment are arranged in 3 layers:

1. **Superficial layer:** Pectineus, adductor longus and gracilis
2. **Intermediate layer:** Obturator externus and adductor brevis
3. **Adductor magnus**

Other Important Points about Medial Thigh Muscles

- **Adductor magnus** is **largest** muscle of medial compartment.
- **Tibial collateral ligament** is degenerated tendon of **adductor magnus**.
- The main function of all above muscles is **adduction of hip joint**.
- All these muscles are supplied by **obturator nerve (1, 2, 3, 4)**
 - **Anterior division** of obturator N.-supplies pectineus, adductor longus, brevis and gracilis.
 - **Posterior division** of obturator N. supplies obturator externus and ischial head of adductor magnus.

POSTERIOR THIGH MUSCLES

1. Biceps femoris
2. Semitendinosus
3. Semimembranosus
4. Ischial head of adductor magnus

Other Important Points about Posterior Thigh Muscles

- The above muscles together are called the **hamstrings**. To be called a hamstring, the muscle must have the following features:
 - Origin from **ischial tuberosity**
 - Insertion into either **tibia or fibula**
 - Nerve supply by **tibial part of sciatic nerve (L5, S1, 2)**; (short head of biceps is supplied by peroneal part of sciatic nerve).
 - **Extensor of hip joint** and **flexor of knee joint**.

EXTRA EDGE

- With Knee semiflexed to 90 degrees, the semitendinosus and semimembranosus act as medial rotators of knee joint; hence called '**medial hamstrings**'.
- With Knee semiflexed to 90 degrees, the long head of biceps femoris acts as lateral rotator of knee joint; hence called '**lateral hamstrings**'.
- **Sacrospinous ligament** is the degenerated tendon of **long head of biceps femoris**.

MUSCLES OF ANTERIOR COMPARTMENT OF LEG

1. Tibialis anterior
2. Extensor hallucis longus
3. Extensor digitorum longus
4. Peroneus tertius.

Other Important Points about Anterior Leg Muscles

- Anterior compartment is also called '**extensor compartment**'.
- All these muscles take origin from fibula **except tibialis anterior** from tibia.
- All these muscle are supplied by **deep peroneal nerve**.
- All these muscles are **dorsiflexors** of the foot (at the ankle joint). In addition,
 - **Tibialis anterior** is an **inverter** of the foot and provides support to **medial longitudinal arch** of foot.
 - **Peroneus tertius** is an **evertor**.
 - Extensor hallucis longus **extends the great toe**.

Radiographic Cassette

- Around the ankle the deep fascia is thickened to form **retinacula**
- **Superior extensor retinaculum** passes between the distal parts of shaft of tibia and fibula.
- **Inferior extensor retinaculum** is Y shaped with the stem of the Y lying laterally and branches of the Y lying medially.
- Structures present deep to extensor retinaculum are the same as structures in anterior aspect of ankle and already discussed with mnemonic under 'ankle joint'.

MUSCLES OF LATERAL COMPARTMENT OF LEG

1. Peroneus Longus
2. Peroneus Brevis

Other Important Points About Lateral Leg Muscles

- Lateral compartment is also called "**peroneal compartment**".
- Both muscles are supplied by **superficial peroneal nerve**.
- Both muscles are **evertors of the foot**.
- Peroneus **brevis** inserts on **tuberosity at base of 5th metatarsal bone**.
- Special features of Peroneus longus are:
 - It provides support to **lateral longitudinal arch** of foot.
 - Its **tendon crosses sole** obliquely from **lateral to medial side** deeply **grooving plantar surface of cuboid bone**.
 - Common, superficial and deep peroneal nerves lie deep to it at the neck of the fibula.
 - **Fibular collateral ligament** is a degenerated part of peroneus longus.

MUSCLES OF POSTERIOR COMPARTMENT OF LEG

1. Superficial muscles are gastrocnemius, soleus, plantaris.
2. Deep muscles are popliteus, flexor digitorum longus, flexor hallucis longus, tibialis posterior.

Other Important Points about Posterior Leg Muscles

- Also called as '**flexor compartment**' of leg since all these muscles are plantar flexors of the foot.
- The **tibial N** supplies all these muscles.
- **Plantar aponeurosis** is a degenerated part of **plantaris** muscle.

- Long and thin **tendon of plantaris** may be mistaken for a nerve by a fresh student doing dissection-hence called "**freshman's nerve**".
- **Tibialis Posterior origin** is from upper 2/3 of posterior surface of interosseous membrane and **inserts** into the **tuberosity of navicular bone**.
- **Popliteus**
 - **Popliteus inserts** into posterior surface of tibia above the soleal line.
 - Tendon of origin of **popliteus** is **intracapsular** (with capsule of knee joint).
 - **Popliteus unlocks the knee joint**.
- The common tendon of flexor digitorum longus receives some fibres (called "**William Turner's slip**") from the tendon of flexor hallucis longus-this inter-tendinous connection helps to strengthen the action of FDL.

Gastrocnemius and Soleus

- Together the two-headed gastrocnemius and soleus form '**triceps surae**'.
- **Gastrocnemius** is active during **running and jumping**, whereas **soleus** is a **postural muscle** active during **normal walking**. (You stroll with help of soleus BUT win running race and long jumps with help of gastrocnemius).
- **Gastrocnemius and soleus** together form the '**calf muscle pump**'.
- **Soleus** is called "**peripheral heart**" since it houses large venous sinuses connected to superficial veins by perforating veins.
- **Tennis leg** = tear of **medial belly of gastrocnemius**.
- **Tendo-Achilles** (Achilles tendon), 15 cm long, is the **thickest and strongest** tendon in the body. It is the common tendon of insertion of gastrocnemius and soleus (ans also plantaris).

Flexor Retinaculum

- **Flexor retinaculum** is a thickened band of deep fascia on the medial side of the ankle.
- Structures under flexor retinaculum are (medial to lateral side or from above downwards)
 - Tibialis posterior tendon
 - FDL tendon
 - Posterior tibial Artery
 - Tibial Nerve and
 - Flexor Hallucis longus tendon.
 - (Mnemonic: "**Tom Dick AN Harry!**")

OTHER IMPORTANT STRUCTURES OF LOWER LIMB

DEEP FASCIA OF THIGH (FASCIA LATA)

- The membranous layer of superficial fascia of thigh is fused with deep fascia of thigh along the **Holden's line**.
- **Iliotibial tract**
 - It is the **thickened part of deep fascia** on **lateral aspect** of thigh.
 - Inferiorly it is inserted into the **lateral condyle of tibia**.
 - Muscles inserted into the iliotibial tract are: **gluteus maximus** and **tensor fascia lata**.
 - Iliotibial tract **stabilises the knee** both in extension and flexion and is therefore used constantly during **walking and running**.
- **Saphenous opening** is the deficiency in deep fascia; it has a sharp and crescentic falciform opening all around **except medial margin** which is ill defined; it is covered by **cristiform fascia** which is **pierced** by the below structures giving a **sieve like appearance**.
 - Long saphenous vein
 - Lymphatics
 - Superficial external pudendal A; Superficial epigastric A; superficial circumflex iliac A (branches of femoral artery).

FEMORAL TRIANGLE

- A.k.a. **Scarpa's triangle**.
- Its apex is below and its limits and floor are as shown in figure below.

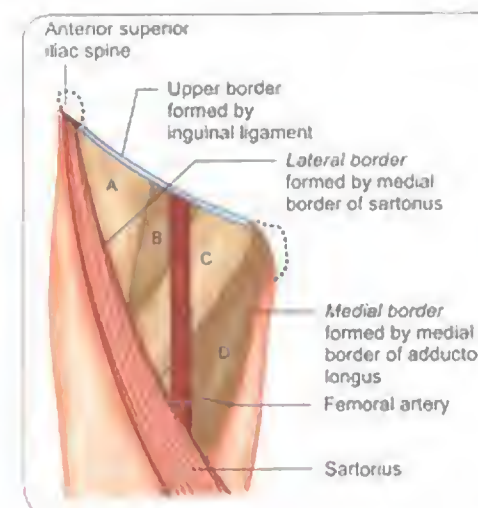


Fig. 2.35: Femoral artery in femoral triangle: The boundaries of the triangle are shown. (A) Iliacus; (B) Psoas major; (C) Pectineus; (D) Adductor longus

- Its contents are
 - Femoral **sheath**
 - Femoral **nerve**, femoral **artery**, femoral **vein**
 - **Lateral cutaneous nerve** of thigh
 - Femoral branch of **genitofemoral nerve**
 - Some **fat** and **deep inguinal lymph nodes**.
- Skin over the femoral triangle is supplied by **genitofemoral nerve**.

FEMORAL SHEATH

- It is a **funnel shaped** envelope around the femoral vessels.
- **Fascia transversalis** forms anterior wall and **fascia iliaca** forms the posterior wall.
- Three compartments of femoral sheath are:
 - **Medial** compartment is **Femoral Canal** containing Lymphatics (discussed below).
 - **Intermediate** canal contains **Femoral Vein**
 - **Lateral** compartment contains **femoral Artery** and **femoral branch of geniofemoral Nerve**. Note: the main femoral nerve is **OUTSIDE** the femoral sheath.
 - Mnemonic: Lateral to medial: "**NAVeL**"; '**e**' stands for 'empty space' (dead space-see below).

FEMORAL CANAL

- The femoral canal occupies the **most medial compartment of the femoral sheath**.
- It extends from the femoral ring above to the saphenous opening below. It is about 2 cm long with its base directed upwards.
- The femoral canal contains **fat, lymphatic vessels and the lymph node of Cloquet**. It provides dead space (empty space) for expansion of femoral vein during times of increased venous return.
- The **femoral ring** is bounded:
 - Anteriorly by the inguinal ligament
 - Posteriorly by **Astley Cooper's (Iliopectineal) ligament**, the pubic bone and the fascia over the pectineus muscle
 - Medially by the **concave knife-like edge of Gimbernat's (lacunar) ligament**, which is also prolonged along the ilio-pectineal line as **Astley-Cooper's ligament**.
 - Laterally by a thin septum separating it from the femoral vein.

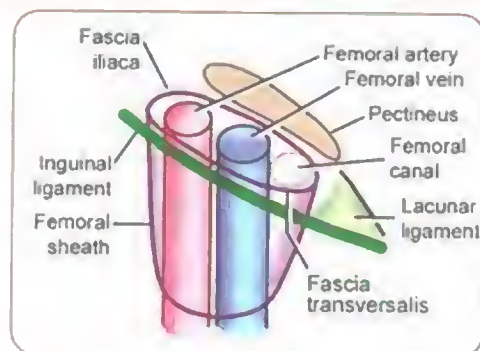


Fig. 2.36: Scheme to show the formation of the femoral canal

EXTRA EDGE

- Femoral canal is an important site of **femoral hernia**; MC in **females** due to greater width of femoral ring.

ADDUCTOR CANAL

- Also called **subsartorial** canal or **Hunter's canal**.
- It extends from apex of femoral triangle to tendinous opening in the adductor magnus through which it opens into the popliteal fossa below.
- Boundaries:**
 - **Anterior:** Vastus medialis
 - **Posterior wall (floor):** Adductor longus above and adductor magnus below.
 - **Medial wall (roof):** Fibrous band with **sartorius** muscle and **subsartorial plexus**.
- Contents:**
 - Femoral artery
 - Femoral vein
 - Saphenous nerve

➤ Nerve to vastus medialis

➤ Note: two terminal branches of obturator nerve and descending genicular artery (from femoral artery) are in the canal for a brief course.

EXTRA EDGE

- In treatment of aneurysm of popliteal artery, the **femoral artery is ligated in the adductor canal**. The principle is that blood still reaches the popliteal artery through anastomotic channels around the knee. This procedure was popularised by John Hunter-hence also called Hunter's canal.

POPLITEAL FOSSA

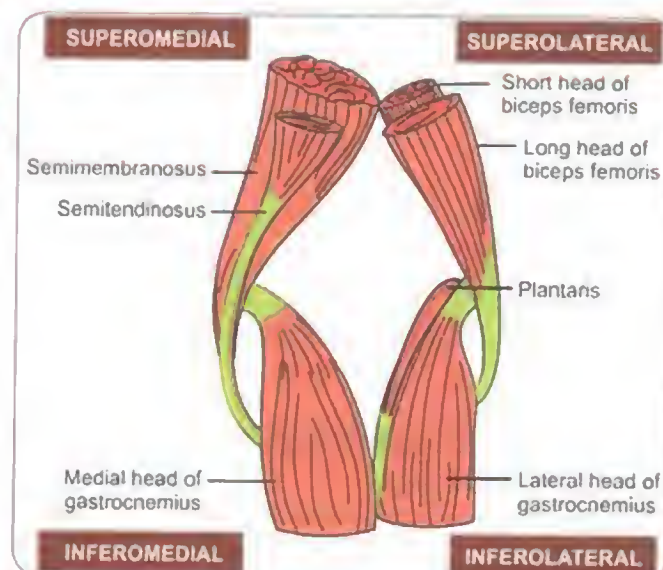


Fig. 2.37: Boundaries of right popliteal fossa

NERVES OF THE LOWER LIMB

FEMORAL NERVE

- Largest** branch of lumbar plexus; root value: **L2,3,4**.
- The **femoral nerve is lateral** to upper part of femoral artery;
- Branches of femoral nerve are:
 - From **main trunk**: nerve to **iliacus**, nerve to **popliteus**
 - From **anterior division**: medial and intermediate femoral cutaneous nerve of thigh
 - From **posterior division**: **saphenous** nerve; nerve to quadratus femoris
 - **Articular** supply: **Hip** joint is supplied by nerve to **rectus femoris**; **knee** joint is supplied by nerve to **three vasti**.

Saphenous Nerve

- Branch of **posterior division** of femoral nerve
- Longest cutaneous nerve** in the body
- It runs **with the great saphenous vein** along the medial side of the leg, passes **in front of medial malleolus** and runs upto the base of the big toe.

EXTRA EDGE

- Saphenous nerve can be injured in front of medial malleolus during venesection of great saphenous vein.
- Femoral nerve damage can cause **sensory loss** over area of **great saphenous vein**.
- Saphenous nerve is used for **nerve grafting**.

OBTURATOR NERVE

- Root value: **L2,3,4**.
- Chief nerve of **adductor (medial)** compartment of thigh.
- The obturator nerve terminates into anterior and posterior division in the **obturator canal**.
- Branches of obturator nerve are mentioned below.
- Obturator nerve supplies **both hip and knee joint**; hence in diseases of hip joint pain may be referred to knee joint.

Anterior division

- Muscular branches to **pectineus**, adductor longus, adductor brevis and gracilis.
- Posterior branch to **hip joint**.
- Vascular branch to **femoral artery**.

Posterior division

- Muscular branches to **obturator externus**, adductor magnus (adductor head)
- Articular branch: **genicular** branch to **knee joint**

SACRAL PLEXUS

Sacral plexus is formed from ventral (anterior) rami of **L4, L5, S1, S2, S3, S4** spinal nerves.

Nerve	Root value	Innervates
Superior Gluteal	L4, L5, S1	Abductor muscles of the thigh (Gluteus medius, Gluteus minimus and tensor fascia lata)
Inferior Gluteal	L5, S1, S2	Extensor of the hip joint (Gluteus maximus)
N. to piriformis	S1, S2	Abductor and rotator of thigh (piriformis)
N. to quadratus femoris	L4, L5, S1	Rotators of thigh (quadratus femoris, gemellus inferior)
N. to obturator internus	L5, S1, S2	Rotators of thigh (obturator internus, gemellus superior)
Perforating cutaneous N	S2, S3	Skin over medial surface of buttock
Posterior cutaneous femoral	S1, S2, S3	Skin over lateral surface of buttock, anal region, upper posterior surface of thigh, upper aspect of calf, scrotum in male and labia majora in female
Sciatic	L4, L5, S1, S2, S3	Composed of 2 nerves (tibial and common fibular); splits into two portions at popliteal fossa: branches from sciatic in thigh region to 'hamstring muscles' and adductor magnus muscle

Contd...

Nerve	Root value	Innervates
Pudendal	S2, S3, S4	Skin of penis and scrotum in male and skin of clitoris, labia majora, labia minora and lower vagina in female, muscles of perineum

SCIATIC NERVE

- Thickest nerve** in the body (1.5-2 cm wide) and **largest branch** of **sacral plexus**.
- Root value: **L4, L5, S1, S2, S3**.
- The main trunk of sciatic nerve has two components:
 - **Tibial** component is **medial** (L4, L5, S1, S2, S3)-supplies all the hamstring muscles
 - **Common peroneal** component is **lateral** component (L4, L5, S1, S2)-supplies **short head of biceps femoris**.
- It has wide sensory supply which includes the entire leg and foot except the area supplied by the saphenous nerve and posterior cutaneous nerve of thigh.
- Sciatic nerve **divides** at the upper angle of popliteal fossa into **tibial** and **common peroneal** nerve.

COMMON PERONEAL NERVE

- Root value: **L4, L5, S1, S2**; a.k.a **lateral popliteal nerve**.
- Common peroneal nerve **winds around the neck of the fibula**-thus injuries around the neck of fibula cause common peroneal nerve palsy. Its branches are:
 - Lateral cutaneous nerve of calf
 - Peroneal communicating branch
 - Branches to ankle joint
- Common peroneal nerve terminates by dividing into **superficial** and **deep** peroneal nerve.
- Superficial peroneal nerve** (a.k.a **superficial fibular nerve**) is the nerve of the **lateral compartment** of the leg and supplies the **peroneus longus** and **peroneus brevis**.
- Deep peroneal nerve** (a.k.a **anterior tibial nerve**):
 - It is the nerve of **anterior compartment** of leg and dorsum of foot. It supplies muscles of anterior compartment: **EHL**: **EDL**; **peroneus tertius** and **tibialis anterior**.
 - It also supplies the skin of adjacent sides of first and second toes-i.e., the **first interdigital cleft**.

Contd...

EXTRA EDGE

- **Common peroneal nerve injury (fibular neck injury)** results in
 - **Foot drop**; weakness of **ankle dorsiflexion** and weakness of **extension of toes** (due to paralysis of muscles of anterior compartment)
 - **Loss of eversion** (due to paralysis of peroneus longus and brevis)
 - **Sensory loss** along anterior and lateral side of leg, dorsum of foot and toes including medial side of big toe
- **NOT affected** are:
 - **Plantar flexion and inversion** (hence can result in equinovarus deformity)
 - **Ankle reflex**
 - Sensation along **lateral border of foot and lateral side of little toe** (supplied by sural nerve) AND **medial border of foot upto ball of big toe** (supplied by saphenous nerve).

TIBIAL NERVE

- Root value: **L4, L5, S1, S2, S3**; A.k.a **medial popliteal nerve** and **posterior tibial nerve**.

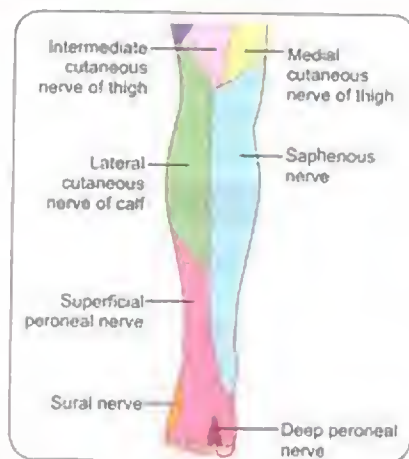


Fig. 2.38: Cutaneous nerve supply of the front of leg and the dorsum of foot

- It is the nerve of **posterior compartment of leg and sole** of the foot.
- Branches in **popliteal fossa** are:
 - **Five muscular branches**: to lateral and medial head of gastrocnemius, soleus, plantaris and popliteus.
 - Articular branches to knee joint
 - **Cutaneous branch-Sural nerve**-supplies the skin of **lower half of back of leg and entire lateral border** of foot till tip of little toe.
- **Note**: Sural nerve runs with short saphenous vein behind lateral malleolus WHEREAS saphenous nerve runs along with long saphenous vein in front of medial malleolus.
- Branches in the leg
 - **Four muscular branches**: nerves to soleus, tibialis posterior, FDL and FHL
 - **Cutaneous: medial calcaneal branches** supplying skin of the heel and posterior part of the sole.
 - **Terminal branches** are the **medial and lateral plantar nerves** supplying the skin of sole and small muscles of the sole.

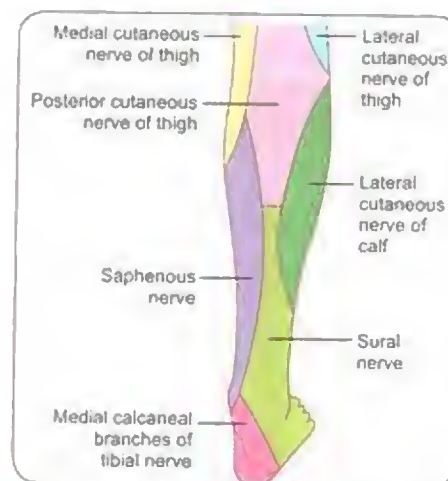


Fig. 2.39: Cutaneous nerve supply of the back of leg

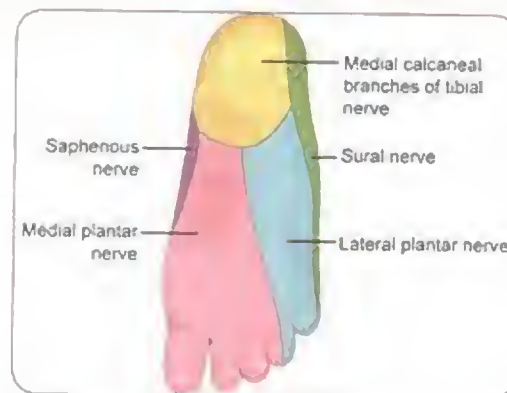


Fig. 2.40: Nerves supplying the skin of sole

VESSELS OF THE LOWER LIMB

FEMORAL ARTERY

- It begins as a **continuation of external iliac artery** at the mid inguinal point (mid point between ASIS and symphysis pubis). It leaves the thigh through the **adductor hiatus** (a tendinous opening in the **adductor magnus** muscle) and it continues further as **popliteal artery**.
- Branches of femoral artery in **femoral triangle** are:
 - Superficial branches:
 - Superficial **external pudendal**
 - Superficial **epigastric**
 - Superficial **circumflex iliac**
 - Deep branches:
 - **Profunda femoris**
 - **Deep external pudendal**
 - Muscular branches
- Branches in **adductor canal** are: **descending genicular artery**.

Profunda Femoris

- **Largest** branch of femoral artery
- It arises from lateral side of femoral artery **4 cm below** inguinal ligament
- Its branches are:
 - **Medial circumflex femoral** (supplies **head of femur**)
 - **Lateral circumflex femoral**
 - **Four perforating arteries** (**2nd perforating artery** gives **nutrient artery to femur**)

POPLITEAL ARTERY

- It is continuation of femoral artery at the level of the **adductor hiatus** in the **adductor magnus** muscle.
- It terminates the lower border of popliteus by dividing into **anterior and posterior tibial** arteries.
- Branches of popliteal A are:
 - **Superior muscular branches** to hamstrings
 - **Sural arteries** supply soleus, gastrocnemius and plantaris muscle.
 - **Five genicular branches** to knee joint (lateral and medial superior genicular A; lateral and medial inferior genicular A, and middle genicular A.)

ANTERIOR TIBIAL ARTERY

- It is the **smaller terminal branch** of popliteal artery; it terminates at the middle of the lateral and medial malleoli, where it continues as **dorsalis pedis** artery of foot. This in turn enters the sole and ends by completing the **plantar arch medially**.

- **Branches of anterior tibial artery** are:
 - Anterior and posterior genicular branches for knee anastomosis.
 - Muscular branches to anterior compartment of leg
 - Anterior medial and anterior lateral malleolar arteries
- **Branches of dorsalis pedis** artery are:
 - Lateral tarsal artery
 - Medial tarsal artery
 - Arcuate artery
 - **First dorsal metatarsal** artery

POSTERIOR TIBIAL ARTERY

- It is the **larger terminal branch** of popliteal artery; it terminates into **lateral and medial plantar arteries** deep to the **flexor retinaculum**.
- **Lateral plantar artery** terminates as **plantar arch** (and is joined by dorsalis pedis which completes the arch).
- Branches of posterior tibial artery are:
 - Circumflex fibular artery
 - **Nutrient artery of tibia**
 - Muscular branches for muscles of back of leg
 - Medial malleolar branch
 - Medial calcaneal branches
 - **Peroneal artery (largest branch)** -
 - Supplies peroneal muscles of lateral compartment
 - Gives **nutrient artery to fibula**.

EXTRA EDGE

- Anterior tibial (**dorsalis pedis pulse**) pulse is felt at the midpoint of the front of the ankle.
- **Posterior tibial pulse** is palpated against the calcaneus about **2 cm below and behind** the medial malleolus.

GREAT (LONG) SAPHENOUS VEIN

- **Longest vein** of the body; "saphenous" means "**easily seen**" since it lies in superficial fascia.
- **Formed by union of medial end of dorsal venous arch** with **medial marginal vein** (dorsal vein of great toe).
- It ascends **anterior to medial malleolus** and accompanied by **saphenous nerve**.
- It ends by piercing the cribriform fascia of the saphenous opening and **terminates into the femoral vein**.
- A valve guarding the saphenofemoral junction is located **4 cm inferolateral** to pubic tubercle.
- Tributaries of saphenous vein are in table below:

In the leg

- Anterior leg vein
- Posterior arch vein (vein of Leonardo da Vinci)
- Vein from the calf

In the thigh

- Anterior cutaneous vein of thigh
- Accessory saphenous vein

Just before piercing cribriform fascia

- Superficial epigastric
- Superficial circumflex iliac
- Superficial external pudendal

Just before termination

- Deep external pudendal

- In the leg it ascends **lateral to tendocalcaneus** and terminates into the **popliteal vein**.

PERFORATING VEINS (PERFORATORS)

There are about 5 veins which connect great saphenous vein to deep veins of leg and thigh by piercing the deep fascia. They contain valves and allow blood to flow only from superficial to deep veins

Location	Connections
Between medial malleolus and mid calf (ankle perforators of Cockett)	Posterior arch vein to posterior tibial artery
Knee or Upper end of calf (tibial tubercle perforator or Boyd's perforator)	Great saphenous vein to posterior tibial artery
Middle third of thigh (Hunterian perforator or Dodd's perforator)	Great saphenous vein to femoral vein in subsartorial canal (this perforator passes through roof of adductor canal)

SMALL (SHORT) SAPHENOUS VEIN

- **Formed by** union of lateral end of dorsal venous arch with lateral marginal vein.
- It enters back of leg by passing **posterior to lateral malleolus** and is accompanied by **sural nerve**.

THORAX**BONES OF THE THORAX****RIBS**

- There are **12 pairs** of ribs. **All** are connected to the thoracic vertebrae in the back.
- There is an increase in size of the ribs from first rib to seventh and decrease from the seventh to twelfth ribs. Thus **7th rib is longest**.

Classification of ribs

- **Floating ribs:** 11th and 12th ribs are **floating ribs** i.e. anteriorly they are free at their ends (**vertebral ribs**).
- **Typical ribs:** 3rd to 9th ribs, which have similar features.
- **Atypical ribs** are 1st, 2nd, 10th, 11th and 12th ribs which have special features.
- **True Ribs:** 1st to 7th ribs are **true ribs** because they articulate with the sternum directly through their costal cartilages (**vertebrosternal ribs**).
- **False ribs:** 8th, 9th and 10th ribs are **false ribs** because they do NOT articulate with the sternum (anteriorly they are joined to the cartilage of the rib immediately above-**vertebrochondral ribs**).
- **Floating ribs:** 11th and 12th ribs are **floating ribs** i.e. anteriorly they are free at their ends (**vertebral ribs**).
- **Typical ribs:** 3rd to 9th ribs, which have similar features.
- **Atypical ribs** are 1st, 2nd, 10th, 11th and 12th ribs which have special features.

Typical Rib

- Typical rib has 3 joints:
 - **Costochondral joint** (between anterior end of rib and its costal cartilage);
 - **Costotransverse joint** (between tubercle of ribs with transverse process of vertebra);
 - **Costovertebral joint** (between head of ribs and corresponding vertebra).
- Posterior end has head, neck, tubercle
- Shaft is long and flat and curved like letter "C".
- A short distance in front of the tubercle, the rib shows a bend marked by a rough line-this point is the **angle of the rib**, where the rib is weakest and hence liable to fracture.

Atypical Ribs—First Rib

- **First rib** is **shortest, broadest and most curved** of the ribs.
- Anterior relations of the neck of the first rib: Sympathetic chain; highest intercostal Vein; superior intercostal Artery; ventral ramus of T1 spinal Nerve. ("Sitting in the VAN")

- The neck of first rib and its anterior relations are closely related to apex of the lung.
- **Scalene tubercle** is present on inner border of 1st rib. The vascular groove **Posterior** to scalene tubercle is for groove is for subclavian Artery and **Anterior** groove is for subclavian Vein and ("PAAV").

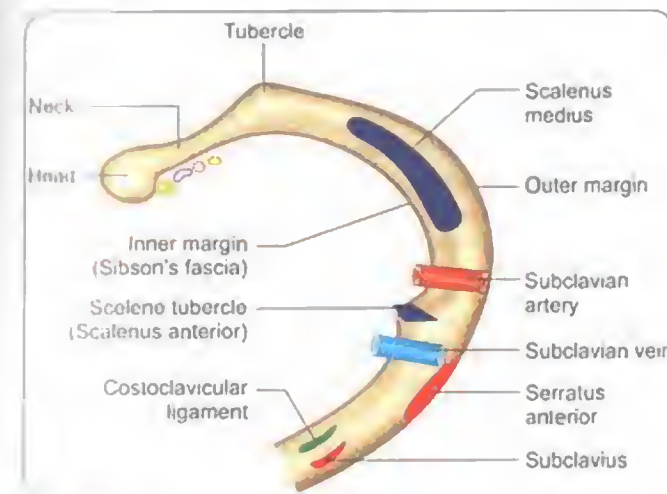


Fig 2.41: Parts of typical rib, attachments and relations of its superior surface and relations of the anterior surface of its neck

- **Attachments on first rib:**
 - Scaleneus anterior and Scaleneus medius
 - Subclavius
 - Serratus anterior (first digitation)
 - Suprapleural membrane (Sibson's fascia)
 - Costoclavicular ligament.

Other Atypical Ribs

- The length of **2nd rib** is **twice** that of first rib.
- **Attachments to 2nd rib** are: scaleneus posterior, serratus anterior (first 2 digitations); serratus posterior superior.
- 10th rib shows all features of a typical rib except that it is shorter.
- 11th and 12th ribs are floating ribs and present only in the posterior abdominal wall. Both ribs are **related posteriorly to left kidney**, BUT **only 12th rib is related to right kidney**. So in operations on kidney the last two ribs are important landmarks.

STERNUM

- The sternum consists of **manubrium, body and xiphoid process**.
- **Manubrium**

- Manubrium is upper **broadest and thickest** part of sternum
- Superior border of manubrium is notched called **jugal notch** or **suprasternal notch of Burns**.
- Two muscles (**sternomastoid** and **pectorals major**) originate from the **anterior surface** of manubrium and two muscles (**sternohyoid** and **sternothyroid** from its **posterior surface**)
- Inferior margin of manubrium articulates with body of sternum-manubrio-sternal joint; angulation of sternum here is called **sternal angle of Louis (160 degrees)**.
- **Left brachiocephalic vein** is in danger during **sternal puncture**.
- **Body of sternum**
 - Formed by union of 4 sternbrae.
 - Provides origin to **pectoralls major** muscle on either side anteriorly.
 - Left and right margins of the body provide articulations with costal cartilages of **2nd to 7th ribs**.
- **Xiphoid process**
 - This is the lower tapering part of the sternum.
- **Joints of the sternum**
 - **Sternoclavicular** joints and sternocostal joints (from 2nd to 7th) are **synovial joints**.
 - **Manubriocostal joint** (**first sternocostal joint**) is a primary cartilaginous joint (**synchondrosis**)
 - **Manubriosternal** joints is a secondary cartilaginous joint (**symphyses**)
 - **Xiphisternal joint** is a secondary cartilaginous joint that turns into a **synostosis** by age of 40 years.
- **Vertebral levels of parts of sternum**
 - Upper margin of manubrium: **T3**
 - Lower margin of manubrium: **T4** (Lower margin)
 - Body of sternum is **T5-T9**.
 - Xiphisternal joint: **T9**

Ossification of sternum

- Ossification occurs by **6 centres**; one for manubrium; 4 for body and one for xiphoid process.
- The body is completely ossified by about **25 years**.
- The xiphoid process unites with the body at about **40 years**.
- Manubrium does NOT fuse with the body; hence manubriosternal joint persists as cartilaginous throughout life.
- **See attached figure** for self explanatory details.

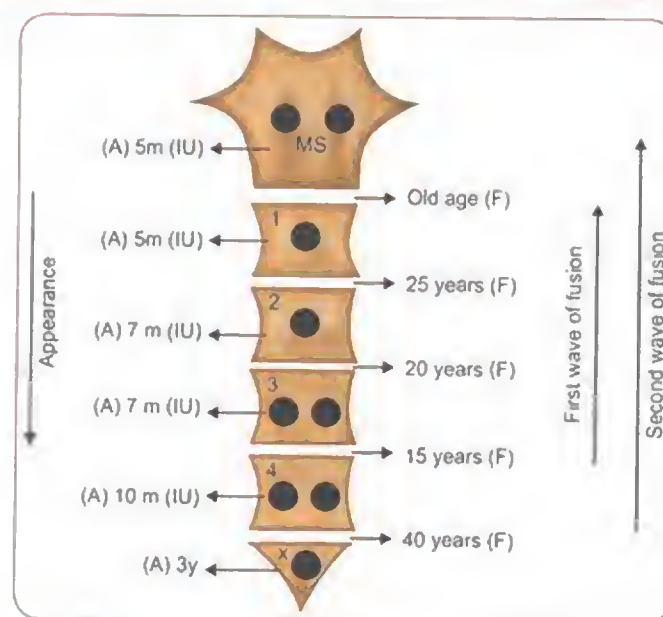


Fig. 2.42: Sternum-ossification center

THORACIC INLET

- Boundaries of thoracic inlet are:
 - Posteriorly: Body of T1 vertebra

MUSCLES, VESSELS AND NERVES OF THE THORAX

MUSCLES OF CHEST WALL

- Intercostal muscles
- Subcostal muscles
- Transversus thoracis
- Levatores costarum
- Serratus posterior

Intercostal Muscles

- From superficial to deep these are:
 - External intercostals
 - Internal intercostals
 - Innermost intercostals (consist of sternocostalis, intercostalis intimus, and subcostalis from before backwards)
- The neurovascular plane of the intercostal space lies **between the internal intercostal and innermost intercostal muscle** (intercostalis intimus muscle).
- The intercostal muscles receive nerve supply from corresponding intercostal nerves.
- "VAN" = relationship of structures in the costal groove (from above down is posterior intercostal Vein, Artery,

- laterally: Inner margins of first ribs and their costal cartilages on either side
- Anteriorly: Upper margin of manubrium sterni.

Structures Passing Through Thoracic Inlet

- Midline Structures**
 - Two strap muscles of the neck (sternohyoid and sternothyroid)
 - Inferior thyroid veins
 - Trachea and esophagus
- Structures on Both Sides of the Midline**
 - Apex of lung and cervical pleura with Sishan's fascia
 - 4 structures anterior to neck of first rib and posterior to lung apex: Sympathetic chain; highest intercostal Vein; superior intercostal Artery; ventral ramus of T1 spinal Nerve
 - Internal thoracic artery, Vagus nerve and phrenic nerve descend medial to lung apex
 - Subclavian vessels
 - Scaleneus anterior and medius muscles
 - Brachiocephalic artery and right brachiocephalic vein on right side of the midline and left common carotid artery, left brachiocephalic vein, left recurrent laryngeal nerve and thoracic duct on left side of midline.

Nerve). (BUT note that this arrangement is **NOT** present in the **first intercostal space**-where a "NAV" arrangement is present).

Respiratory movements

- Inspiration**
 - **Chief muscle** of inspiration: **Diaphragm**
 - **Accessory muscles** of inspiration: external intercostal muscles and interchondral portion of internal intercostals
 - Muscles of **forced inspiration**: Scaleneus anterior, sternomastoid, pectoralis muscles, serratus anterior, serratus posterior, quadratus lumborum.
- Expiration**
 - **Quiet expiration** is a **passive process** by elastic recoil of lungs and of costal cartilage and relaxation of diaphragm
 - **Forced expiration**: an active process involving anterior abdominal wall muscles assisted by **erector spinae, serratus posterior inferior and latissimus dorsi**.

BLOOD VESSELS OF CHEST WALL

Arterial Supply

- the **upper nine** intercostal spaces contain three arteries, **two Anterior** intercostal arteries **one Posterior** intercostal artery ("AAP").
- The **10th and 11th spaces** contain **ONLY** a **single posterior intercostal artery**.
- Posterior Intercostal artery**
 - It is the main artery of intercostal space
 - The **1st and 2nd** posterior intercostal arteries are branches of **superior intercostal artery** (which is a branch of **costocervical trunk of the subclavian artery**)
 - The lower nine (**3rd to 11th**) posterior intercostal arteries arise directly from **descending thoracic aorta**.
- Anterior Intercostal artery**
 - In **1st to 6th** space, the anterior intercostal arteries are branches of **internal thoracic artery** on each side
 - In **7th to 9th** spaces, they are branches of **musculophrenic artery** on each side.
- Internal thoracic artery**: A.k.a **internal mammary artery**; it is a **branch of first part of subclavian artery** in the neck. It descends and terminates in the **6th intercostal space** by dividing into **superior epigastric** and **musculophrenic** arteries.
- Branches of internal thoracic artery:
 - **Anterior intercostal arteries**-one pair per space in the first 6 intercostal spaces.
 - Pericardiophrenic branch
 - Mediastinal branches
 - Sternal branches
 - Perforating branches

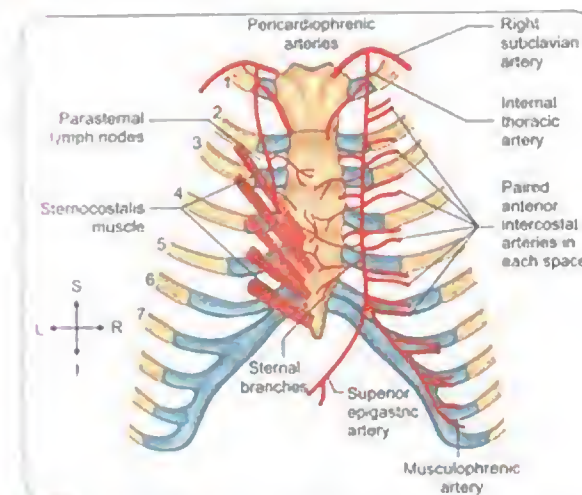


Fig. 2.43: Internal thoracic (mammary) artery viewed from the inner aspect of the anterior thoracic wall (Note that sternocostalis muscle is shown only on the left side)

Venous Drainage

- The **upper nine** intercostal spaces contain **two Anterior** intercostal veins **one Posterior** intercostal vein. ("AAP") and the **10th and 11th spaces** contain **ONLY** a **single posterior intercostal vein**-similar to arterial supply.
- Posterior intercostal vein** of 1st space is also called **highest intercostal vein** and drains into the **brachiocephalic vein**.
 - **2nd to 4th** posterior intercostal veins unite to form **superior intercostal vein** which drains into **azygos vein** on right side and into **left brachiocephalic vein** on left side.
 - On right side **5th to 11th** posterior intercostal veins drain into **azygos vein**.
 - On left side, **5th to 8th** posterior intercostal veins drain into **accessory hemiazygos vein** and **9th to 11th** posterior intercostal veins drain into **hemiazygos vein**.
- Anterior intercostal veins** of 7th to 9th space drain into **musculophrenic vein** (a tributary of internal thoracic vein). 1st to 6th anterior intercostal veins drain directly into internal thoracic vein.

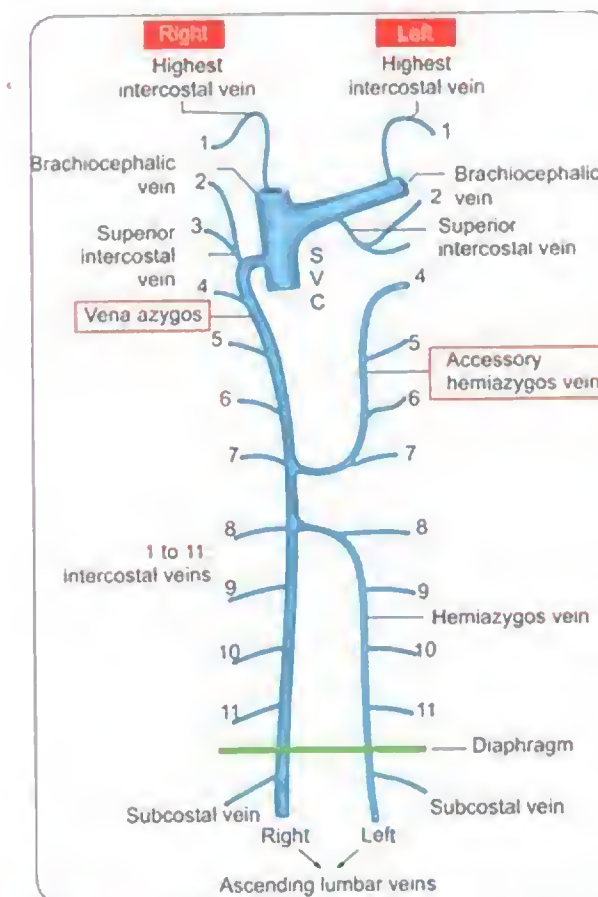


Fig. 2.44: Veins of thoracic wall (1 to 11 are posterior intercostal veins)

NERVES OF CHEST WALL

- **Ventral rami** of upper 11 thoracic spinal nerves (T1-T11) are called **intercostal nerves** and T12 is called **subcostal nerves** (since it runs along **lower border of 12th rib**).
- Upper 6 intercostal nerves supply thoracic wall whereas lower 5 intercostal nerves and subcostal nerves supply the thoracic and anterior abdominal wall—**thoracoabdominal nerves**.
- **Lateral cutaneous branch of 2nd intercostal nerve** forms **intercostobrachial nerve** supplying medial surface of upper arm and axilla.
- The **intercostobrachial nerve** is at risk of damage during axillary lymph node dissection BUT risk is much less with sentinel lymph node biopsy.
- **Typical intercostal nerves** are those that are confined to their own intercostal space—example—3rd, 4th, 5th and 6th intercostal nerves.
- **Atypical intercostal nerves** extend beyond the thoracic wall for distribution partly or entirely—example—1st, 2nd and 7th-11th intercostal nerves.

THORACIC DUCT

- A.k.a **Pecquet duct**; **largest lymphatic duct** in the body about **45 cm long**.
- Thoracic duct begins as a **continuation of the upper end of cisterna chyli** near **lower border of T12 vertebra**.
- It enters the thorax through the **aortic opening of diaphragm** at T12.
- It then ascend through the posterior mediastinum and at **T5 level crosses from the right side to left side**.

- At the level of C7 vertebra, it arches towards left side to **open into the left brachiocephalic vein** at the angle of union of left subclavian and left IJV.
- Thoracic duct receives lymph from **both halves of the body below the diaphragm** and the **left half above the diaphragm**. Its tributaries are:
 - Right and left lumbar trunk
 - In thorax: posterior mediastinal nodes, small intercostal lymph nodes.
 - In neck: left jugular trunk, left subclavian trunk and left bronchomediastinal trunk.

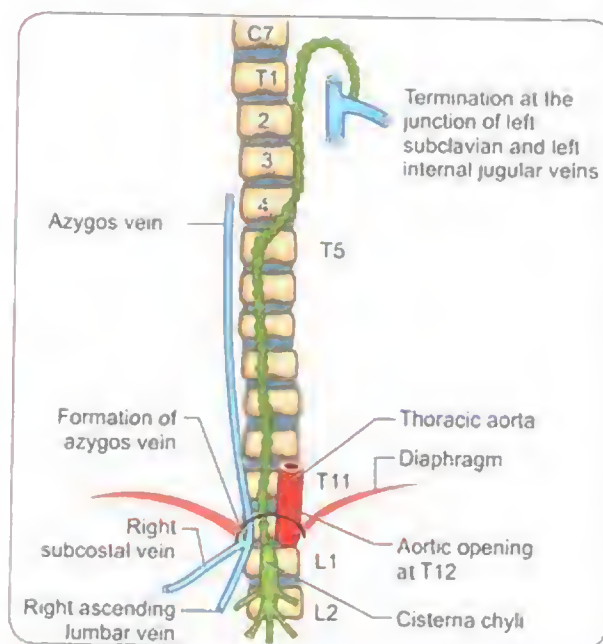


Fig. 2.45: Thoracic duct

RESPIRATORY APPARATUS

BASICS ABOUT AIRWAYS

- **Weibel's classification**: Between the trachea and alveolar sacs, the airways divide about **23 times**.
- **Conducting zone**:
 - This includes the **first 16 generations** of airways
 - Consists of the **bronchi** (upto 10th generation) and **terminal bronchioles** (from 11th to 16th generation).
 - As there is no alveoli upto 16th generation, gas exchange does NOT occur in the conducting zone.
 - So the volume from the nose to 16th generation airways is called **anatomic dead space**.
- **Respiratory zone**:
 - The last 7 generations of airways form the respiratory zone—**respiratory bronchioles** (17th to 19th); **alveo-**

lar ducts (20th-22nd generation) and **alveolar sac** (23rd generation).

- Respiratory zone is the site for **gas exchange**.
- **Alveoli**
 - Alveolus is the **functional unit** of gas exchange.
 - There are **300 million alveoli in humans** and the total area of the alveolar walls in contact with capillaries in both lungs is about **70 sq.m.**—thus **alveoli** are the **largest biological membrane** in the body.
 - Types of alveolar cells are:
 1. **Type 1 cells**—cover **90-95%** of alveolar surface
 2. **Type 2 cells** (a.k.a type 2 **pneumocytes** or **granular pneumocytes**)—secrete **surfactant**; are more **metabolically active** and contain **lamellar inclusion bodies**.

- 3. Other cells: **pulmonary alveolar macrophages** (**dust cells**)—**phagocytic** function.

EXTRA EDGE

- By definition—airways **lacking cartilaginous plates** and submucosal glands are **bronchioles**.
- **Largest amount of smooth muscle** relative to the thickness of the wall is present in the **terminal bronchioles**.
- **Cilia** are present upto respiratory bronchioles.
- **Clara Cells** (nonciliated cell) present in bronchioles secrete surfact protein (SP-B)

TRACHEA

- Length = **10-16 cm** (12 cm)
- The external diameter of trachea in adult male and female = 2 cm and 1.5 cm respectively.
- Internal diameter = 1.2 mm in adult and about 3 mm in newborn.
- It commences at the **larynx (C6)** and **bifurcates** into the main bronchi (**at lower border of T4**).
- At tracheal bifurcation, the lower margin of lowest cartilaginous ring is called **carina**; it is **25 cm from incisor teeth** and a useful landmark during bronchoscopy.
- Lined with **pseudostratified ciliated columnar epithelium**.
- There are about **15-20 incomplete C-shaped cartilaginous rings** which reinforces the anterior and lateral sides of the trachea to **protect and maintain the airway open**.
- The **cricoid cartilage** is a "**signet ring**" shaped ring of hyaline cartilage located at the inferior aspect of the larynx and is the **ONLY complete ring of cartilage** around the trachea.
- There is a piece of smooth muscle connecting the ends of the incomplete cartilaginous rings called the **trachealis muscle**. This contracts reducing the size of the lumen of the trachea to **increase the air flow rate during coughing**.
- The **esophagus** lies **posteriorly** to the trachea. The cartilaginous rings are incomplete because this allows the trachea to collapse slightly to allow food to pass down the esophagus.
- Blood supply of trachea:
 - **Upper 2/3** by **inferior thyroid artery**
 - **Lower 1/3** by **bronchial artery**.
 - Tracheal veins drain into inferior thyroid venous plexus.

BRONCHI

- The **trachea divides** at the level of lower border of **T4 vertebra** into two principal bronchi.
- The **right bronchus** divides into **epiarterial** and **hyparterial** bronchi before entering the hilum whereas the left bronchus enters as such.
- **Right main bronchus**: wider, shorter (2.5 cm), more vertical (25 degrees with median plane). Right main bronchus divides into **3 lobar bronchi**. Right lower lobar bronchus is most vertical almost continuous in direction with the trachea. **Hence inhaled foreign body** is more likely to enter the **right main bronchus** and lodges **MC in superior segment of right lower lobe**. ("If you accidentally inhale a bite, it goes down the right!").
- **Left main bronchus**: narrower, longer (5 cm), more horizontal. The left main bronchus divides into **2 lobar bronchi**.
- The lobar bronchi divide into **tertiary (segmental) bronchi**.
- Beyond the tertiary bronchi, the C-shaped cartilaginous rings are replaced by **plates and islands of cartilage**. As the bronchi divide further there is a decrease in the amount of cartilage and increase in the amount of smooth muscles in the airways.
- The part of the lung aerated by tertiary bronchus is called a **bronchopulmonary segment** (see below).

BRONCHOPULMONARY SEGMENT

- A bronchopulmonary segment (BPS) is the largest subdivision of a lobe of a lung that is separated from the rest of the lung by a connective tissue septum.
- This property allows a **BPS to be surgically removed without affecting other segments**.
- Each BPS has a **tertiary (segmental) bronchus** and **2 arteries (bronchial and pulmonary)** in the center; veins and lymphatics drain along the borders.
- Each BPS is **drained by intersegmental parts of the pulmonary veins** that lie in the intersegmental space and drain adjacent segments.
- BPS is NOT a bronchovascular segment since it does not have its own vein.
- BPS is **named according to the segmental bronchus supplying it**.
- Each lung has **10 BPS**.
- BUT, some authorities consider the **left lung to have 8 BPS** since there are 2 regions in the left lung which have 2 segments joined as 1 since they share the same tertiary (segmental) bronchus—"left upper lobe **apicoposterior**" and the "left lower lobe **anteromedial** segment".

- BPS of the right and left lungs are shown in below table.

Right lung		
Upper Lobe	Middle Lobe	Lower Lobe
Apical	Medial	Superior
Posterior	Lateral	Medial basal
Anterior		Anterior Basal
		Lateral Basal
		Posterior basal

Left lung	
Upper Lobe	Lower Lobe
Apicoposterior	Anteromedial
Superior Lingular	Lateral basal
Inferior Lingular	Posterior
Anterior	Superior

EXTRA EDGE

- Mnemonic of BPS for right lung is "A PALM Seed Makes Another Little Palm".
- Mnemonic of BPS for left lung is "ASIA ALPS".
- The **superior (apical) BPS** of lower lobe is the **most dependent** in supine position and secretions tend to collect in it.

PLEURA

Visceral (pulmonary) pleura	Parietal pleura
<ul style="list-style-type: none"> • It is firmly adherent to the lung surface (inseparable) • It develops from splanchnopleural mesoderm. • It is pain insensitive • It is innervated by autonomic nerves. 	<ul style="list-style-type: none"> • It lines the walls of the pulmonary cavity. • It develops from somatopleural mesoderm. • It is pain sensitive and • It is supplied somatic nerves (by intercostal and phrenic nerves)

Subdivisions of Parietal Pleura

1. **Costal (costovertebral) pleura**: lines the inner surface of thoracic wall to which it is attached by a thin layer of loose areolar tissue called **endothoracic fascia** (analogous to **transversalis fascia** of abdominal wall). Superior to first rib, the **costal pleura is continuous with the cervical pleura** and inferiorly with the diaphragmatic pleura.
2. **Diaphragmatic pleura** covers the superior surface of diaphragm.
3. **Mediastinal pleura**: at the root of the lung it becomes continuous with visceral pleura. The **pulmonary ligament** is not a true ligament but rather the reflection of the **mediastinal parietal pleura** below the lung root on each side.

4. **Cervical pleura**: extends into the root of the neck (1 inch above medial end of clavicle and 2 inches above first rib).

- The **costodiaphragmatic line of pleural reflection** (inferior margin of pleura) crosses the 8th rib in the mid-clavicular line, 10th rib in the mid-axillary line, 12th rib at the lateral border of sacrospinalis muscle (8, 10, 12) and ends posteriorly 2 cm lateral to spinous process of T12 vertebra.
- **Costodiaphragmatic recess** is the **first part of pleural cavity to be filled by pleural fluid in pleural effusion**. Vertically it extends from 8th to 10th rib in midaxillary line.
- **Costomedial recess** lies anteriorly between costal and mediastinal parietal pleura.

Pleural tapping (Thoracentesis)

- The **neurovascular bundle** of the intercostal space is situated **just below the upper rib**. Hence in pleural tapping, the **needle is inserted just above the upper border of the rib** (lower part of intercostal space).
- Tapping of pleural fluid is usually done in **mid-axillary line** in lower part of **6th intercostal space**.
- **Layers of chest wall pierced** during tapping are shown in attached figure: skin, superficial fascia, serratus anterior muscle, intercostal muscles (3 layers), endothoracic fascia and parietal (costal) pleura.

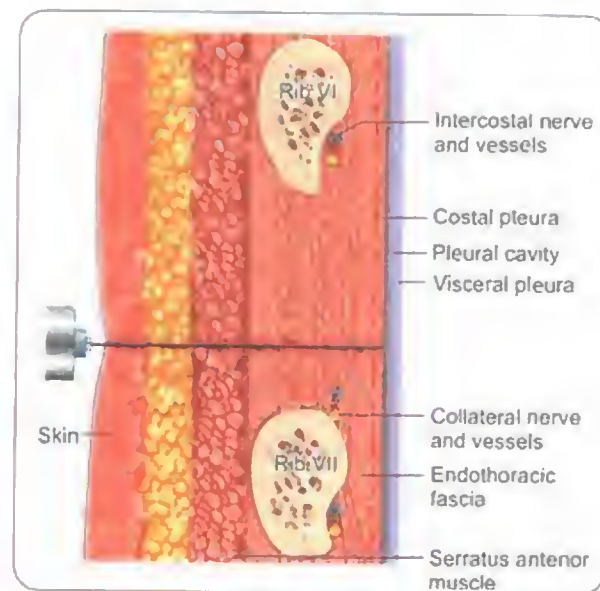


Fig. 2.46: Layers of chest wall pierced in succession by the needle inserted for pleural tapping along the posterior axillary line

LUNGS

Right lung	Left lung
<ul style="list-style-type: none"> • Is divided into 3 lobes (superior, middle, inferior) by two fissures—horizontal and oblique. • Weighs about 625 gm, 50 gm heavier than left lung • An Azygos lobe is a congenital variation of the Right Upper Lobe 	<ul style="list-style-type: none"> • Is divided into 2 lobes (superior and inferior) by an oblique fissure. • The tongue shaped projection of the Upper Lobe of left lung below the cardiac notch is called lingula. ("Lingula in Left Upper Lobe")

EXTRA EDGE

- The relations of structures at hilum of two lungs are different.
- Structures from above downwards in the right lung are eparterial **Bronchus**, pulmonary **Artery**, hyparterial **Bronchus** and inferior pulmonary **Vein**. In left lung they are pulmonary **Artery**, principal **Bronchus** and inferior pulmonary **Vein**.
- To remember the above-mnemonic—"Left lung asks the question—Are Beasts Violent? and right lung replies—Beasts Are Born Violent!"

Structures Related to the Medial Surface of the Lungs

- **Right lung**: Right atrium and auricle; right ventricle (partly), SVC, right brachiocephalic vein, azygos vein, esophagus, IVC, trachea, right vagus and right phrenic nerve
- **Left Lung**: Left ventricle, Left auricle, infundibulum, right ventricle (partly), pulmonary trunk, arch of aorta, descending thoracic aorta, thoracic duct, left subclavian artery, esophagus, left brachiocephalic vein, left superior intercostal vein, left vagus and phrenic nerves, and left recurrent laryngeal nerve.

Relations of Apex of Lung

- **Anteriorly**: Subclavian artery, subclavian vein and scalenus anterior muscle
- **Posteriorly**: sympathetic chain; highest intercostal vein; superior intercostal artery; ascending branch of ventral ramus of T1
- **Laterally**: scalenus medius muscle
- **Medially**:
 - On right side from anterior to posterior—right brachiocephalic vein; right phrenic nerve; brachiocephalic artery; right vagus and trachea
 - On left side—from anterior to posterior—left brachiocephalic vein, left subclavian artery, left recurrent laryngeal nerve, esophagus and thoracic duct.

Pancoast syndrome

- When structures in posterior relation of lung apex are involved due to lung cancer—signs and symptoms which occurs are called Pancoast syndrome
- Pain in ulnar distribution and wasting of small muscles of hand (due to injury to ventral ramus of T1 or lower trunk of brachial plexus)
- Horner's syndrome—due to injury to sympathetic chain
- Erosion of first and second ribs.

Blood Supply of Lungs

- Bronchial arteries supply intrapulmonary bronchial tree and blood for nutrition of the lung;
- **Right bronchial artery** (1 in number) is a branch of the **3rd posterior intercostal artery**
- Left **bronchial artery** (2 in number) is **derived from descending thoracic aorta**.
- **Right bronchial veins** drain into the **azygos vein**, the **left bronchial vein** drain into the **hemiazygos vein**.

DIAPHRAGM

Openings in the Diaphragm

IVC opening

Present in the **central tendon** portion on the **right side of midline** at **T8** vertebral level.

Structures passing are:

- Inferior Vena cava (IVC)
- Branches of **Right** phrenic N.

Oesophageal opening

Present in the **muscular portion** by **splitting of fibres of right crus** at **T10** vertebral level on **left side of midline**.

Structures passing are:

- Esophagus
- Right and Left Vagus N.
- Oesophageal branch of left gastric A.
- Accompanying veins and lymphatics.

Aortic opening

Present in **midline** between **diaphragmatic crura** at **T12** vertebral level. Structures passing are:

- Aorta
- Azygos V
- Thoracic duct
- Hemiazygos V (passes through left crus)
- Sympathetic trunk (passes behind medial arcuate ligament)
- **Left** phrenic N. (pierces the muscle of left dome)
- Subcostal N. and Vessels (pass behind lateral arcuate ligament)

EXTRA EDGE

- Some Mnemonics for above table:
 - "IOA-Indian Olympic Association-T8, T10, T12-Inferior Vena cava, Oesophagus, Aorta";
 - "Both **vagus** go with Oesophagus!";
 - "For Indian ViCtory (IVC) ... in war...we need **Right Phren**ds (phrenic)!"
- Nerve supply of diaphragm-**Phrenic nerve (C3,4,5)**-"**C3,4,5 keeps the diaphragm alive!**".
- Superior epigastric vessels** pass through a gap (**space of Larry**) between sternal and costal slips of origin of diaphragm from seventh costal cartilage.

PERICARDIUM

- Pericardium is a sac covering the heart and consists of:
 - **Outer fibrous pericardium**

- **Inner serous pericardium** consisting of inner visceral pericardium (epicardium) and outer parietal pericardium.
- **Pericardial cavity** is a potential space between the parietal and visceral layers of serous pericardium. Normally it contains about **50 ml** of fluid.
- Blood supply of pericardium: pericardiophrenic branches of **internal thoracic artery**.
- Nerve supply by **phrenic nerves**.

Pericardial sinuses

- Due to folding and bending of the heart tube, two potential spaces come to exist in the pericardial cavity-these are the pericardial sinuses-**oblique sinus** and **transverse sinus**.
- **Transverse sinus** provides space during **cardiac surgery** to clamp the ascending aorta and pulmonary trunk in order to insert tubes of heart lung machine in these vessels.

HEART

External Features of Heart

- Heart is placed obliquely in the **middle mediastinum**.
- Approximately **2/3** of heart is to the left and **1/3** to the right of the midline.
- The heart makes an angle of **45 degrees** with sagittal plane.
- The weight of adults heart is **250-300 grams**.
- Three sulci** are atrioventricular sulcus (coronary sulcus), interatrial sulcus and interventricular sulcus.
- The point of junction of posterior atrioventricular, interatrial and posterior interventricular sulci is called "**crux**" of the heart.
- There are 4 margins/borders-superior, inferior (acute), right and left (obtuse). Inferior (acute) margin is formed mainly by right ventricle.
- Apex** is the **most mobile** part of the heart; it is directed, downward, forward and to the left.
- Left ventricle** has 3 times **thicker wall** than right ventricle.
- Right atrium** is **thinnest** of the four chambers
- Right ventricle** is in **contact with the sternum**.

Surfaces of Heart

- **Anterior or sternocostal surface:** formed mainly by right ventricle and minorly by right atrium and left ventricle

- **Inferior or diaphragmatic surface:** formed by left ventricle (left 2/3) and right ventricle (right 1/3).
- **Posterior surface (Base):** formed by left atrium (left 2/3) and right atrium (right 1/3).

Interior of Right Atrium

- Right atrium has 2 parts
 - **Sinus venarum** (smooth part) located posteriorly (derived from right horn of sinus venosus)
 - **Right atrium proper along with right auricle** (rough part); (derived from common atrial chamber of cardiac tube).
- Features of sinus venarum
 - Opening of **SVC** at roof
 - Opening of **IVC** located lowest and posterior part of right atrium
 - Opening of **coronary sinus** located between opening of IVC and tricuspid orifice
 - Multiple small openings of **venae cordis minimae** (smallest cardiac veins or Thebesian veins) are seen in all chambers of the heart.
- Features of right atrium proper and auricle (rough part)
 - **Crista terminalis** demarcates rough and smooth parts of right atrium
 - **Musculi pectinati** are parallel muscular ridges extending from the crista into the right auricle; ense trabeculations of musculi pectinati are a potential site for thrombus formation.
 - **Anterior cardiac veins** open here

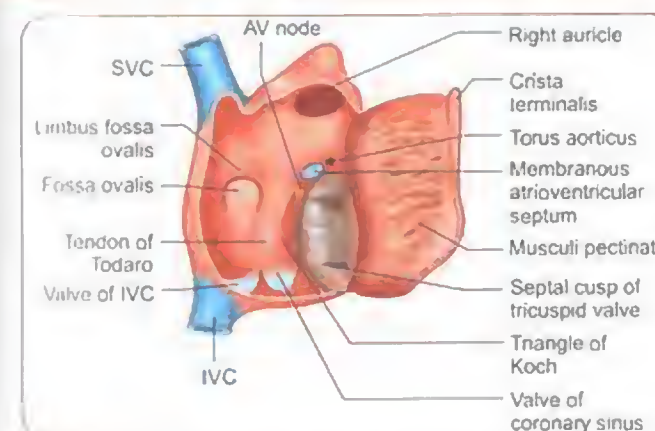


Fig. 2.47: Right lateral view of opened right atrium to depict internal features

Key: AV node: Atrioventricular node; SVC: Superior vena cava; IVC: Inferior vena cava

EXTRA EDGE

- **Koch's triangle** is an identifiable landmark in the right atrium during surgery.
- It has 3 boundaries-the valve of coronary sinus (posteriorly); tendon of Todaro (superiorly) and the attached margin of the septal cusp of tricuspid valve (anteriorly).
- The **AV node** lies at **apex of Koch's triangle**, which is a feature of floor of right atrium near the lower end of interatrial septum.

Interatrial Septum

- Interatrial septum develops from approximation of embryonic **septum primum** and **septum secundum**.
- Features of the right atrial side are:
 - **Fossa ovalis:** Oval shaped depression lying **above the level of the IVC opening** in the interatrial septum; it is embryonic remnant of foramen ovale; floor of fossa ovalis represents **septum primum**.
 - **Limbus fossa ovalis:** a thickened rim present above the fossa ovalis; represents the lower free margin of septum secundum.

Interior of Right Ventricle

- Right ventricle has 2 parts:
 - **Trabecular body** (ventricle proper) is the rough outflow part
 - **Infundibulum** (conus arteriosus) is the smooth outflow part.
- Features of right ventricle proper
 - The cavity of right ventricle proper (Trabecular body) is characterised by muscular projections called

trabeculae carneae-there are 3 types viz. ridges, bridges and papillary muscles.

- The **ridges** are found all over the cavity in large numbers
- The **bridges** are elevations which are fixed at two ends but remain free in between-**septomarginal trabecula (moderator band)** is the best example; this passes from IV septum to base of anterior papillary muscle; it carries the right branch of atrioventricular bundle (**RBB**) in its substance. This ensures early contraction of papillary muscles so that chordae tendinae are already taut before ventricular contraction begins.
- The **papillary muscles** may be anterior, posterior and **septal**. (remember that left ventricle has **ONLY** anterior and posterior papillary muscles!)

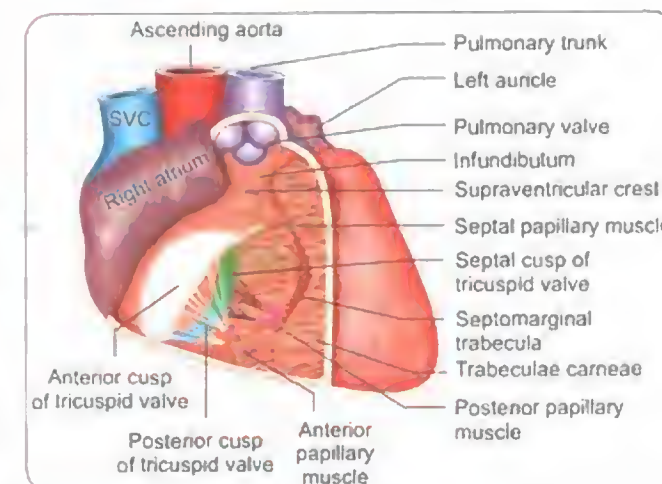


Fig. 2.48: Anterior view of opened right ventricle to depict internal features.

Key: SVC: Superior vena cava

Heart Valves

- Tricuspid valve has 3 leaflets: anterior (largest), septal (smallest) and posterior.
- Mitral valve has 2 leaflets: anterior (larger), posterior (smaller)
- Pulmonary valve has 3 cusps: 1 posterior and 2 anterior
- Aortic valve has 3 cusps: 1 anterior and 2 posterior.

BLOOD SUPPLY OF HEART

Right Coronary Artery (RCA)

- A **branch of the anterior aortic sinus** of ascending aorta.

- It runs in the **right anterior coronary sulcus** (right atrioventricular groove) and then winds round the inferior border to run in the **posterior interventricular groove** where it ends by anastomosing with the left coronary artery.
- Branches of RCA are:
 - **Posterior descending (interventricular) A.** in 90% cases.
 - Acute marginal A.
 - **Nodal branch** to SA node (in 65% cases)
 - **Right (conus) infundibular A.** (sometimes it directly arises from anterior aortic sinus and is called "**third coronary artery!**")

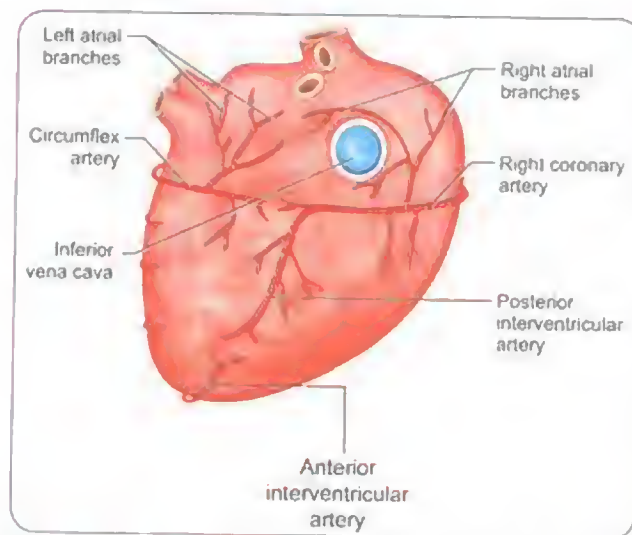


Fig. 2.49: Branches of right coronary artery and of circumflex branch of left coronary artery on the posterior and inferior surfaces of heart

Left Coronary Artery (LCA)

- **Larger** than right coronary artery.
- Arises from the **left posterior aortic sinus** of ascending aorta. It enters the atrioventricular groove and gives anterior interventricular branch. Further continuation of LCA is called **circumflex artery**.
- Branches of the LCA are:
 - **Left anterior descending (interventricular) A.** This is the **MC diseased** coronary artery and most often bypassed during CABG surgery:
 - Circumflex A.
 - Left diagonal A.
 - Obtuse marginal (left marginal) A.
 - Left conus A.
 - Nodal branch (35%) for SA node.

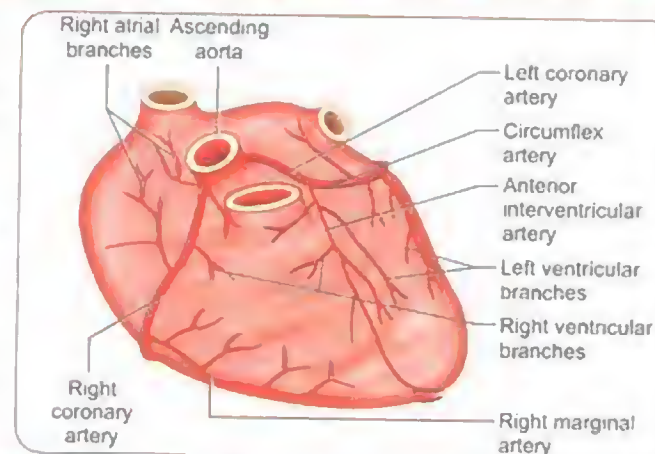


Fig. 2.50: Course and branches of right and left coronary arteries on sternocostal surface (Note the anastomosis of conus arteries on the surface of infundibulum of right ventricle)

Artery	Structures supplied
Right Coronary A.	Right atrium Most of Right ventricle and posterior 1/3 of interventricular septum SA Node (65% cases) AV node Whole conducting system except right bundle branch
Left Coronary A.	Anterior part of right and left ventricle Lateral wall of left ventricle and most of left ventricle Anterior 2/3s of interventricular septum A-V groove. SA node (in 35% of cases) Right bundle branch

Heart—Venous Drainage

- 90% drains into **right atrium through coronary sinus** via the great, middle and small cardiac veins.
- Coronary sinus begins as the continuation of great cardiac vein at left end of coronary sulcus and opens into the smooth part of right atrium. Opening of coronary sinus is located between the opening of IVC and tricuspid orifice and is guarded by a small valve (**Thebesian valve**).
- 10% drains into other **chambers** via the **venae cordis minimis**.
- **Anterior cardiac veins** drain into **right atrium**.
- So the **tributaries of coronary sinus** are:
 - Great cardiac vein: Lies in anterior interventricular groove

- Middle cardiac vein: lies in posterior interventricular groove
- Small cardiac veins
- Posterior vein of left ventricle
- Oblique vein of left atrium (of **Marshall**)
- Left marginal vein
- Veins which **DO NOT** drain into coronary sinus BUT drain directly into right atrium are: **anterior cardiac vein; vena cordis minimae** and often **right marginal vein**.

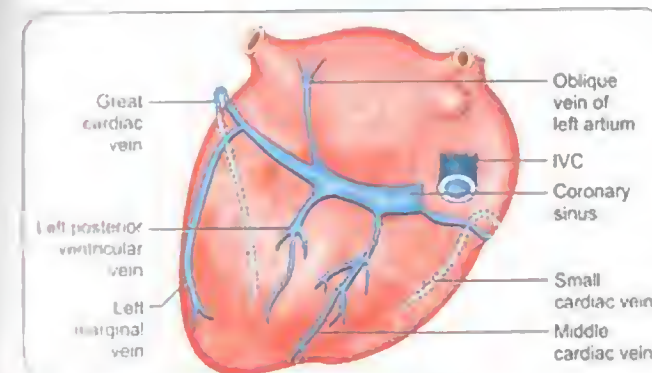


Fig. 2.51: Coronary sinus (continuation of great cardiac vein) and its tributaries viewed from posterior aspect of heart

Key: IVC: Inferior vena cava

EXTRA EDGE

- **Cardiac Dominance:** The question of **anatomical dominance** is determined by the artery that supplies the **posterior descending (interventricular) artery**. **Most commonly** (in 90%), the **posterior descending artery** arises from the **Right Coronary Artery**, a pattern referred to as '**right dominance**'.

CONDUCTING SYSTEM OF THE HEART

The conducting system is made up of specialized myocardium.

- **SA node**
 - SA node is located in the **upper part of the crista terminalis** at the junction of SVC and the right atrium.
 - It is the **primary pacemaker of the heart** and generates impulses at the rate of **70–100/min**.
 - SA node is supplied by the **nodal artery, a branch of the RCA in 65% cases** and a branch of circumflex branch of LCA in 35% cases.
 - Supplied by **right vagus**.

Internodal pathways

- There are **3 internodal pathways** that connect the SA node and AV node:
 1. **Anterior** internodal tract of **Bachman**
 2. **Middle** internodal tract of **Wenckebach**
 3. **Posterior** internodal tract of **Thorel**
- Also, from SA node a conducting tract arises and directly enters into the left atrium—called interatrial tract or **Bachman's bundle**.
- **AV node**
 - It lies in the right atrial floor near the interatrial septum in the '**triangle of Koch**'.
 - It is supplied by **AV nodal artery, a branch of RCA**.
 - Supplied by the **left vagus**.
- **Atrioventricular bundle of His**
 - It has **dual blood supply**—from **AV nodal artery** (branch of RCA) and **anterior descending branch of LCA**.
- **Right Bundle Branch (RBB) and Left bundle branch (LBB)**
 - These bundle branches consist of modified muscle fibres (**Purkinje fibres**).
 - **Both RBB and LBB** are supplied by **LCA (except a small part of LBB supplied by RCA)**.

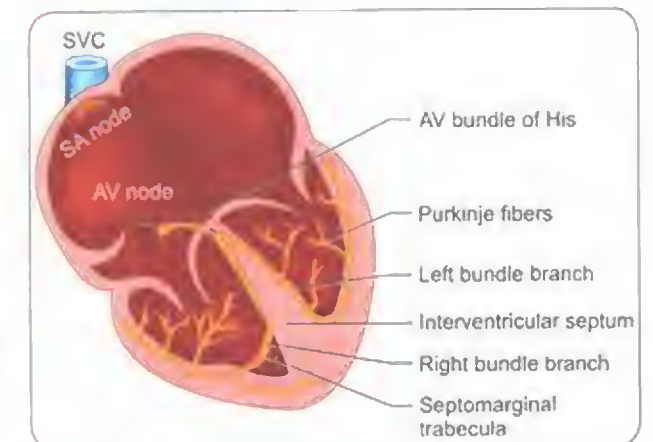


Fig. 2.52: Parts of conducting tissue of heart

Key: SVC: Superior vena cava; SA: Sinoatrial; AV: Atrioventricular

Heart-Nerve Supply

- Parasympathetic: **Cardioinhibitory**
 - **Right vagus:** SA node and atria;
 - **Left vagus:** AV node and conducting tissue.
- Sympathetic: **Cardiostimulatory (excitatory)**
 - Cervical and upper thoracic sympathetic ganglia (T1–T5).

Heart Borders on Chest X-ray

- Right border** Superior vena cava, right atrium and inferior vena cava.
- Left border** Aortic arch, left pulmonary artery, aortic knuckle, left atrial appendage, left ventricle.

High Yield Heart Points

- Torus aorticus** is the prominent region of the **right atrial septum** sited superiorly and anteriorly. It is

superior to the coronary sinus and anterior to the fossa ovalis. It represents the deeper and anterior surface of the posterior sinus and cusp of the aortic valve.

- Valve of Viussens:** Venous valve dividing the great cardiac vein and coronary sinus.
- Leiden convention:** is used in imaging of heart; the artery that arises from the observer's left hand side is the left coronary artery and the other is the right.
- Dicrotic notch** on the aortic pressure curve is caused by the **closure of aortic valve (dicORTic!)**.

ABDOMEN

ANTERIOR ABDOMINAL WALL

Planes of Abdomen

Transpyloric plane (of Addison) (horizontal)

- Passes midway between the suprasternal notch and the symphysis pubis.
- It lies about a hand's breadth below the xiphisternal joint.
- Anteriorly, it passes through the **tips of the ninth costal cartilages**; and posteriorly through the body of **L1 vertebra** (near its lower border)
- The plane passes through the
 - Pylorus of the stomach** (hence called :trans-pyloric!)
 - Duodenojejunal junction,
 - Fundus of gall bladder,
 - Neck of the pancreas
 - Hila of the kidneys
 - Origin of superior mesenteric artery
 - Origin of portal vein
 - Attachment of transverse mesocolon

Transtubercular plane (horizontal)

- Passes through **tubercles of iliac crest** and the body of vertebra **L5** near its upper border.
- IVC** begins; position of **ileocecal** orifice at this level (L5)

Right and left lateral planes (vertical)

- Correspond to **midclavicular** or **mammary lines** indicated by lines drawn on the surface through points halfway between the anterior superior iliac spine and symphysis pubis (mid-inguinal point).

Subcostal plane (horizontal)

- Passes through the **lower borders of the 10th costal cartilage**, and **body of vertebra L3** (near its upper border)

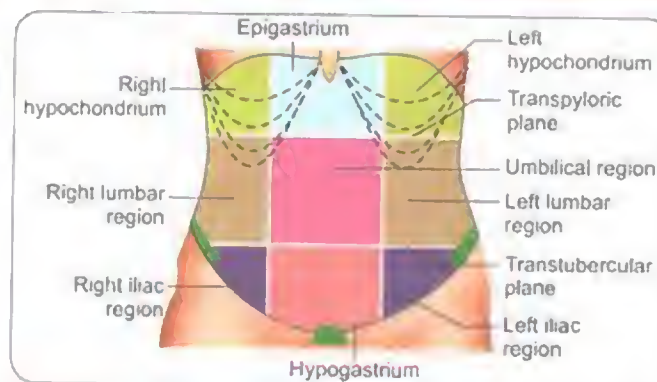


Fig. 2.53: Regions of anterior abdominal wall

Layers of Anterior Abdominal Wall

- Skin
- Superficial fascia
- External oblique
- Internal oblique
- Transversus abdominis
- Transversalis fascia
- Extraperitoneal tissue
- Peritoneum

Fascia of anterior abdominal wall

- The superficial fascia of the anterior abdominal wall is divided into a **superficial fatty layer (fascia of Camper)** and a **deep membranous layer (fascia of Scarpa)**.
- In the midline, the membranous layer (Scarpa) is continuous below with a similar membranous layer of the superficial fascia of the perineum (**Colle's fascia**) and below and laterally it **blends with the fascia lata** of the thigh a little below the inguinal ligament.

Cutaneous Nerves of Anterior Abdominal Wall

- Lower five intercostal nerves (T7-T11), subcostal (T12) and the iliohypogastric (L1) nerves supply the skin through their cutaneous branches.
- T7 dermatome** is located over the **xiphoid process**.
- T10 dermatome** overlies **skin around the umbilicus**.
- L1 dermatome** lies on **pubic symphysis and inguinal ligament**.
- The pain of **appendicitis** is referred to **T10 dermatome**.

Disorders at Umbilicus

- Urinary fistula** at umbilicus: Due to **persistent urachus**.
- Faecal fistula** at umbilicus: Due to **persistent patent vitellointestinal duct**
- Umbilical adenoma: Raspberry tumour**; may result from unobliterated vitellointestinal duct
- Sister Joseph's nodule: Metastatic gastric adenoCa.** at umbilicus

MUSCLES OF ABDOMINAL WALLS

External Oblique

- Supplied by **T7-T11 and T12** (subcostal) nerves.
- Modifications of the external oblique aponeurosis are: **inguinal ligament**, **lacunar ligament** and **reflex inguinal ligament**.
- Superficial inguinal ring** is an opening in external oblique aponeurosis.
- The external oblique aponeurosis prolongs around the spermatic cord from the margins of the superficial inguinal ring as the **external spermatic fascia**.

Internal Oblique

- Located internal to external oblique muscle.
- Supplied by **T7-T11 and T12** (subcostal) nerves; **iliohypogastric** (L1) and **ilioinguinal** (L1) nerves.
- Cremaster** muscle and cremasteric fascia are **derived from internal oblique** muscle, BUT it is supplied by **genital branch of genitofemoral N. (L1, L2)**; It **pulls up the testis** towards the superficial inguinal ring.
- Cremasteric reflex**—on stroking skin of medial side of upper thigh, there is reflex elevation of testis on stimulated side; **afferent** is ilioinguinal nerve (L1) and **efferent** is genitofemoral nerve (L1, L2).

Transversus Abdominis

- Deepest** muscle of anterior abdominal wall.
- Supplied by **T7-T11 and T12** (subcostal) nerves; **iliohypogastric** (L1) and **ilioinguinal** (L1) nerves—similar to internal oblique.
- Neurovascular bundle of anterior abdominal wall** lies **between it and internal oblique**.
- The lower fleshy fibres of internal oblique and transversus abdominis muscles fuse to form the **conjoint tendon (falx inguinalis)** behind the medial end of inguinal canal. The conjoint tendon is attached to pubic crest and pecten pubis. **Weakened conjoint tendon** predisposes to **direct inguinal hernia**.

Actions of Anterior Abdominal Wall Muscles

- They give **support to abdominal viscera**.
- Contraction of these muscles **increases intra-abdominal pressure** that pushes up the diaphragm and helps in forceful expulsive/inspiratory acts like **micturition, defecation, parturition, coughing, sneezing**.
- Lateral flexion** of trunk is by one sided contraction of oblique muscles.
- Flexion of trunk** (lumbar spine) is by rectus abdominis muscles.
- Rotation of trunk** to one side (touching one elbow to opposite knee is rotation) is by opposite sided external oblique and same sided internal oblique—example, **rotation of trunk to right** is by **left external oblique** combined with **right internal oblique**.

Rectus sheath

- The rectus sheath is an aponeurotic covering for the rectus abdominis and pyramidalis muscles on either side of the linea alba.
- Contents of rectus sheath are:
 - Rectus abdominis and pyramidalis muscles
 - Lower 5 intercostal nerves and subcostal nerve
 - Superior and inferior epigastric vessels.

Rectus Abdominis

- Right and left muscles are separated by linea alba.
- Origins is tendinous below and insertion is fleshy above.
- Rectus abdominis has three tendinous intersections that are **attached to anterior abdominal wall**.
- It is **supplied** by lower 5 intercostal nerves and subcostal nerve.
- It is a **flexor** of vertebral column.
- Pyramidalis:** A small muscles situated in front of lower part of rectus muscle. It is a tensor of linea alba and supplied by subcostal nerve (T12).

Note

- The inguinal region anatomy and all related MCQ points has been described in detail in surgery chapter under Inguinal hernia for ease of understanding (Pg 894).

Muscles of Posterior Abdominal Wall

- Quadratus lumborum, Psoas major, Psoas minor, Iliacus.

PERITONEUM

- Peritoneum is the largest serous membrane composed of mesothelial cells (*simple squamous epithelium*). It is divided into:

- **Parietal peritoneum:** Develops from *somatopleuric mesoderm*; pain sensitive.
- **Visceral peritoneum:** Develops from *splanchnopleuric mesoderm*; pain insensitive but it is pain sensitive when *stretched, distended or ischemic* (due to autonomic innervation!).

Retroperitoneal structures

Retroperitoneal organs

- GIT—Almost entire duodenum (except proximal 2 cm); Ascending and Descending colon; Rectum
- Kidneys and Ureter
- Suprarenal glands
- Pancreas

Retroperitoneal structures on posterior abdominal wall

- Abdominal aorta and its branches
- IVC and its tributaries
- Portal vein and its tributaries
- Cisterna chyli and lymph nodes
- Lumbar plexus, sympathetic chains and sympathetic plexuses
- Muscles of posterior abdominal wall

Retroperitoneal structures in pelvis

- Common iliac vessels
- External and internal iliac vessels
- Sympathetic chains
- Sacral and coccygeal plexuses
- Lymph nodes and muscles of pelvis

VARIOUS PERITONEAL FOLDS

Basic Terms

- Peritoneal folds attached to stomach: **Omenta** (greater and lesser, see below)
- Peritoneal folds attached to intestines: **mesentery**; (*mesocolon* for large intestine)
- Peritoneal folds connecting organs to each other OR to abdominal wall are called **ligaments**-ex: lienorenal ligament; gastrosplenic ligament.



Fig. 2.54: Sagittal section of abdominopelvic cavity in male to show peritoneal sacs, folds and pouches

Omenta

Greater omentum

- **Greater omentum** hangs down from greater curvature of stomach.
- It is called "**policeman of abdomen**" since it adheres to area of inflammation wrapping around inflamed organs and localising the infections.
- It is also a **storehouse of fat**.
- "**Milky spots**" present in greater omentum consist of **macrophages** (which help in combating infection once any inflamed organ is wrapped by the greater omentum).

Lesser Omentum:

- **Lesser omentum** extends from stomach (lesser curvature) and duodenum (first 2 cm) to the liver. It has two parts—**hepatogastric** and **hepatoduodenal** ligament.

- **Hepatogastric ligament** forms anterior free margin contains the right and left gastric vessels, branches of gastric nerves and lymph vessels.
- **Hepatoduodenal ligament** forms **right free margin of lesser sac** and contains:
 - Portal vein
 - Hepatic artery,
 - Bile duct.

Mesentery

- Root of mesentery is **15 cm** long and extends from duodenojejunal flexure (on left side of L2) to upper part of right sacroiliac joint.
- Root of mesentery **crosses following structures**:
 - Horizontal (3rd) part of duodenum;
 - Abdominal aorta,
 - IVC,
 - Right ureter
 - Right psoas major
 - Right genitofemoral nerve
- Transverse mesocolon** connects transverse colon to posterior abdominal wall and contains **middle colic vessels**.
- Mesoappendix** connects appendix to ileal mesentery and contains **appendicular vessels**
- Sigmoid mesocolon** connects sigmoid colon to posterior pelvic wall and contains **sigmoid vessels**.
- Mesorectum**: Although the rectum has no mesentery, its surrounding fat is enclosed within a fascial envelop called as mesorectum (**mesorectal fascia** or fascia propria). It is an important surgical and radiological structure well seen on MRI. It contains:
 - **Superior rectal artery.**
 - **Superior rectal vein** and its branches.
 - **Lymph nodes**
 - **Adipose connective tissue**
 - Rectal branches from **inferior hypogastric plexus**.

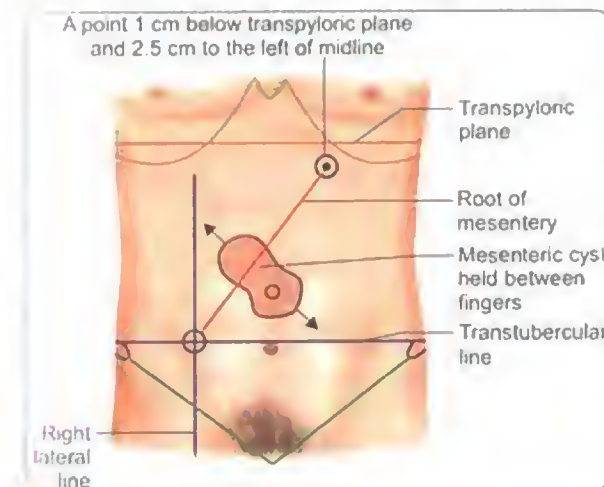


Fig. 2.55: Surface marking of root of mesentery and its clinical significance

Peritoneal Ligaments

- Gastrosplenic ligament**: contains **short gastric vessels** and left gastroepiploic vessels.
- Lienorenal ligament**: contains **splenic vessels** and tail of pancreas
- Gastrosplenic and Lienorenal ligaments** develop from **dorsal mesogastrium**
- Phrenicocolic ligament**: connects left colic flexure to diaphragm; **supports anterior border of spleen**.
- Falciform ligament**:
 - a **stickle shaped** peritoneal fold connecting **anterosuperior surface of liver to anterior abdominal wall and diaphragm**.
 - It demarcates the **right and left lobes** of the liver.
 - Falciform ligament **contains ligamentum teres; paraumbilical vein**.
- Coronary ligament**: encloses '**bare area of the liver**'.
- Triangular ligaments**: connects right and left lobes of liver to diaphragm.
- Falciform, coronary and triangular ligaments** develop from **ventral mesogastrium**.
- Note**: The **spleen** develops within the dorsal mesogastrium, while the **liver** develops within the **ventral mesogastrium**

Derivatives of

Dorsal mesogastrium
Greater omentum
Gastrosplenic ligament
Gastrophrenic ligament
Lienorenal ligament

Ventral mesogastrium
Lesser omentum
Falciform ligament
Coronary ligament
Right and left triangular ligament

PERITONEAL CAVITY

Lesser Sac (Omental Bursa)

- Lesser sac/omental bursa** is also called **left subhepatic space** or **left posterior intraperitoneal space**.
- It lies behind the stomach, lesser omentum and liver.
- It is a closed space except for its communication on right side with greater sac through **epiploic foramen**.
- Boundaries of lesser sac are:
 - **Anterior wall**: Caudate lobe of liver; stomach; lesser omentum and 2nd layer of greater omentum
 - **Posterior wall**: 3rd layer of greater omentum and structures forming stomach bed.

Epiploic Foramen

- A.k.a **foramen of Winslow** or **aditus to lesser sac** or **Duvernoy's foramen**;
- It is a **slit like opening** through which **lesser sac communicates with greater sac**. Located at **T12 level**.
- Its boundaries are:
 - Anterior: **Right free margin of lesser omentum** (containing portal vein, hepatic artery and bile duct)
 - Posterior: IVC; right suprarenal gland and T12 vertebra.
 - Superiorly: Caudate process of liver
 - Inferiorly: First part of the duodenum and horizontal part of hepatic artery.

EXTRA EDGE

- A **posterior gastric ulcer** may perforate into lesser sac. The leaking fluid passes through epiploic foramen to reach the hepatorenal pouch.

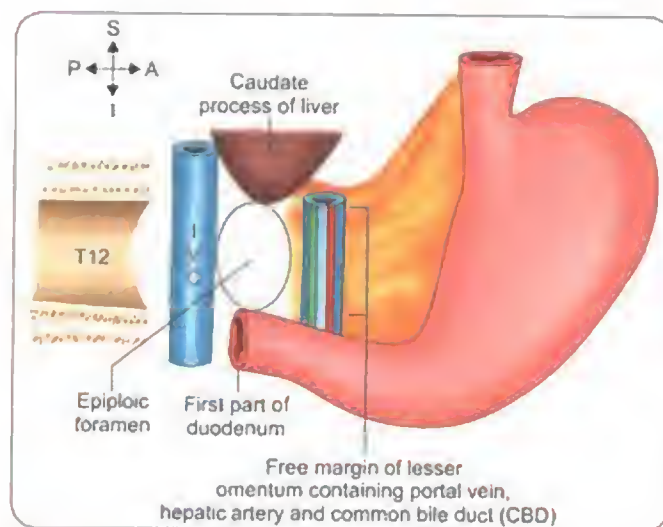


Fig. 2.56: Boundaries of epiploic foramen

GASTROINTESTINAL STRUCTURES

ESOPHAGUS

Note

- Even though esophagus is a major thoracic structure, for the sake of continuity it is discussed here under GIT.
- Esophagus is **25 cm** long; Occupies the **posterior mediastinum**
- Extends from the cricopharyngeal sphincter at the **lower border of cricoid cartilage (at the level of C6 vertebrae)** to the **cardia of the stomach (45 cm from**

Greater Sac

- Greater sac is divided by line of attachment of transverse mesocolon and pelvic brim into 3 parts: **Supracolic** (above transverse mesocolon); **Infracolic** (below transverse mesocolon) and **pelvic** (below pelvic brim).
- **Supracolic compartment** (Subphrenic spaces): These spaces are just below diaphragm in relation to the liver. They are as in below table:

Intraperitoneal spaces	Extraperitoneal spaces
<ul style="list-style-type: none"> • Left anterior space (left subphrenic space) • Left posterior space (left subhepatic space or lesser sac) • Right anterior space (right subphrenic space) • Right posterior space (right subhepatic space or hepatorenal pouch or Morrison's pouch)-it is most dependant part of peritoneal cavity in supine position and MC site for subphrenic abscess 	<ul style="list-style-type: none"> • Right and left extraperitoneal spaces • Midline extraperitoneal space (Bare area of liver)

- **Pelvic Peritoneal cavity:**

- In males rectovesical pouch of peritoneum intervenes between rectum and urinary bladder. Obliterated part of rectovesical pouch is called **fascia of Denonvillier's** which separates posterior surface of prostate from rectum.
- In females, **rectouterine pouch (pouch of Douglas)** lies between **rectum (posteriorly)** and **uterus and posterior fornix of vagina (anteriorly)**.
- These two pouches in males and females respectively are the **most dependant** portion of peritoneal cavity in **erect posture**.

teeth to cardia of stomach); **1.25 cm** of this tube lies below the diaphragm

- Is the **narrowest region of the alimentary tract except for the vermiform appendix**. **Narrowest part** is at its commencement at the **cricopharyngeal sphincter**.
- Lined by **stratified squamous nonkeratinising epithellum** which is replaced by specialised columnar epithelium (lower 3 cm) at the level of the hiatus similar to gastric mucosa but without oxyntic and peptic cells

- **Serosa is absent** in esophagus
- **Angle of His** is the **acute angle** created **between the esophagus and cardia** at the entrance to the stomach.
- **Parasympathetic N. supply: Vagus** through an extrinsic

and intrinsic plexus. The intrinsic plexus has no Meissner's network, which is present elsewhere through the alimentary canal, and only Auerbach's plexus is present.

Constrictions of the Esophagus

Distance from incisor teeth	Structure causing constriction	Problems associated
15 cm (6")	Cricopharyngeal sphincter	Foreign body lodgement
22.5 cm (9")	Aortic Arch	Perforation during endoscopy
27.5 cm (11")	Left main Bronchus	
40 cm (15")	Diaphragm entry	Malignancy

Mnemonic: "**Children And Adults Love Burgers at McDonald's**"; 15; 22.5; 27.5; 40 cm.

Part of Esophagus	Arterial supply	Venous drainage	Type of muscle	Lymphatic drainage
Cervical (Upper 1/3)	Inferior Thyroid A.	Inferior thyroid vein and thence into right/left brachiocephalic vein	Striated	Deep cervical
Thoracic (Middle 1/3)	Thoracic Aorta	Azygos (right side) and hemiazygos (on left side)	Striated/Smooth	Mediastinal
Abdominal (lower 1/3)	Left Gastric A.	Left gastric vein and short gastric veins and thence into coronary vein and thence into portal vein	Smooth	Gastric

EXTRA EDGE

- Mnemonic for arterial supply in above table: "**In Testing Times Always think Life's Good!**"
- The capillaries of the esophagus drain into a **submucosal** and **periesophageal** venous plexus from which the main esophageal veins originate.

STOMACH

- A.k.a "gaster" or "ventriculus"
- It is the **most dilated part** of the alimentary canal.
- Mean capacity is about **30 ul (one ounce)** at birth, **1000 ul at puberty** and about **1500 ml in adults**
- MC shape of the stomach is **J-shaped** (vertically oriented); it may also be horizontally oriented-**steer horn** stomach.
- **Parts of the stomach**
- **Fundus, body and pyloric part** (pyloric antrum, pyloric canal and pylorus).
- A line passing through the **incisura angularis of the lesser curvature** indicates demarcation of body and pyloric part.

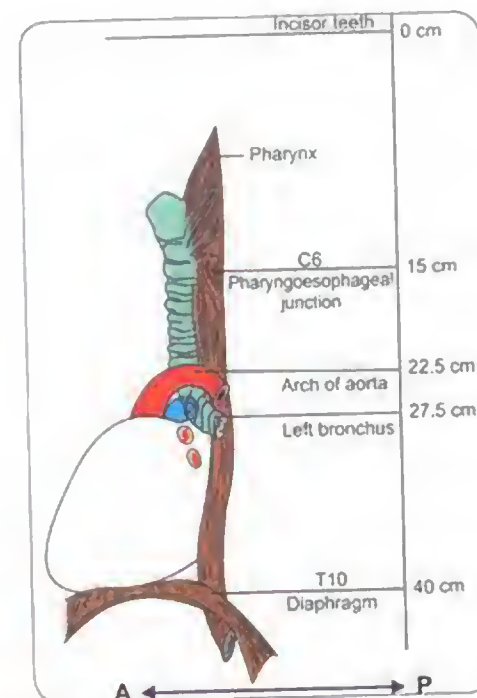


Fig. 2.57: Distances of esophageal constrictions from incisor teeth (Note that vertebral extent of esophagus is from C6 to T11)

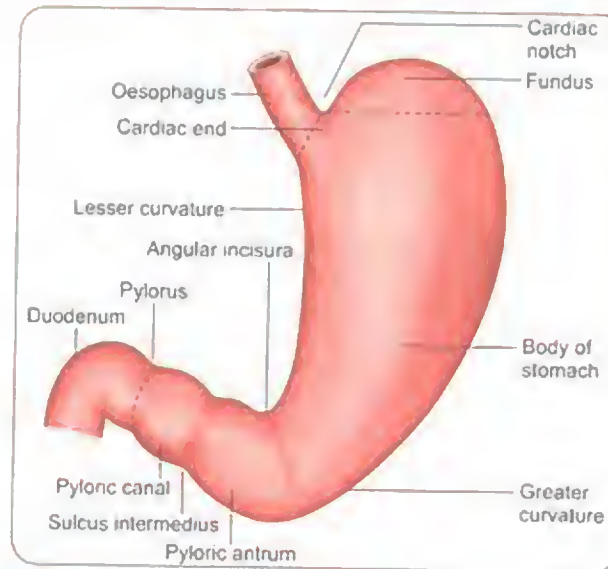


Fig. 2.58: Subdivisions of the stomach

EXTRA EDGE

- **Traube's space:** This area is *tympanic to percussion* and *overlies the fundus* of the stomach. In pleural effusion on left side and hypertrophy of spleen and liver this space is obliterated.
- Boundaries are:
 - Superiorly: lower margin of resonance of left lung
 - On left: by lateral margin of spleen
 - On right: by lower margin of left lobe of liver
 - Inferiorly: by left costal margin

Bed of Stomach

- The postero-inferior surface of the stomach is separated by the cavity of the lesser sac from several structures lying on the posterior abdominal wall-these structures are collectively called **stomach bed**. These are:
 - Left crus and lower fibres of diaphragm
 - Left inferior phrenic vessels
 - Left kidney and left suprarenal gland
 - Anterior surface of pancreas
 - Left colic flexure and transverse mesocolon
 - Spleen
 - Splenic artery.

Arterial Supply of Stomach

Left gastric A. The **smallest** branch of celiac axis BUT the **largest and main artery** supplying the stomach

Contd...

Contd...

Right gastric A.

A branch of hepatic A

Left gastroepiploic A. and short gastric A.

From splenic A

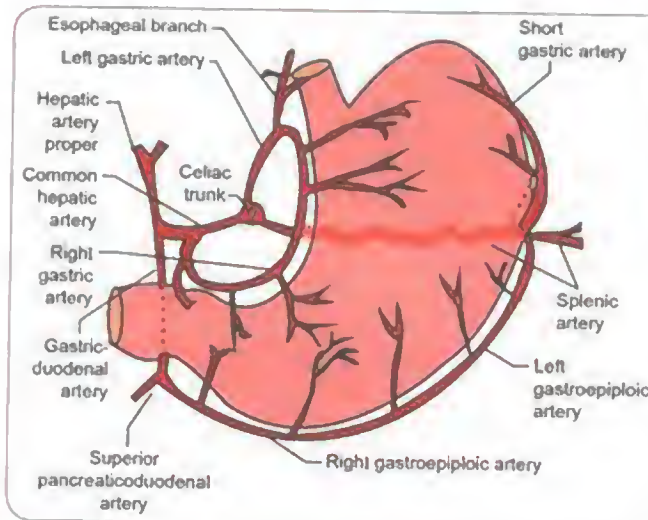
Right gastroepiploic A.Branch of gastroduodenal A (**largest branch of hepatic A**)

Fig. 2.59: Arterial supply of stomach through branches of celiac trunk

Venous Drainage of Stomach

- Right gastric vein and left gastric vein drain into the portal vein.
- Short gastric vein and left gastroepiploic vein drain into splenic vein.
- Right gastroepiploic vein drains into **superior mesenteric vein**.

Nerve Supply of Stomach

- **Sympathetic:**
 - From **coeliac plexus** via greater and lesser splanchnic nerves (T6-T10).
 - Pain sensation is carried by sympathetic fibres and is referred to **epigastric region** (T6-T10).
- **Motor and sensory:**
 - Parasympathetic through **Vagus N.** Vagal stimulation
 - **Increases acid and enzymatic secretion,**
 - **Decreases sphincter tone** and
 - **Increases gastric motility.**
 - The **anterior vagus (left vagus)** divides into anterior gastric and hepatic branches. The main branch of anterior gastric branch (**anterior nerve of Latarjet**) supplies the **body, fundus and pyloric antrum**.

- The **posterior vagus (right vagus)** gives two main branches (posterior nerve of Latarjet) and celiac. The gastric branch supplies upper and posterior part of body of stomach till the pyloric antrum. Its **most cranial branch is called criminal nerve of Grassi** (as it might be missed during vagotomy)!

EXTRA EDGE

- The **nerves of Latarjet** supply the acid and pepsin secreting areas of the stomach.

Lymphatic Drainage of Stomach

- See self explanatory figure below for lymphatic drainage.

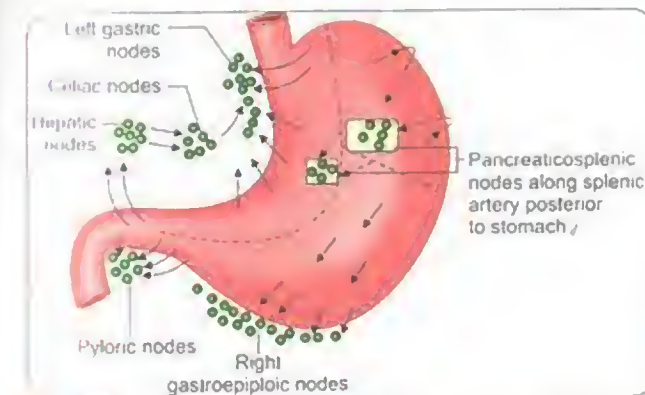
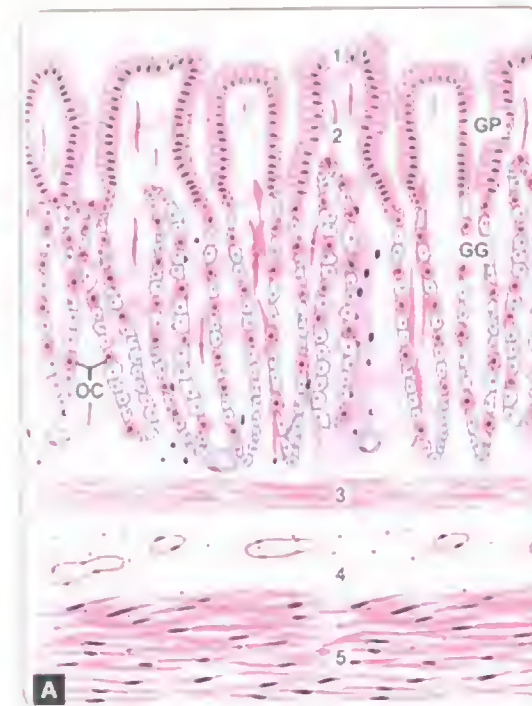


Fig. 2.60: Lymphatic drainage of the various zones of stomach



Figs. 2.61A and B: Stomach (body/fundus). A. As seen in drawing; B. Photomicrograph

DUODENUM

- Duodenum is the **shortest, widest and most fixed** part of small intestine.
- It is **25 cm** long and is mostly **retroperitoneal except proximal 2.5 cm**.
- Duodenum has a **C-shaped curve** enclosing the **head of the pancreas**.
- It is opposite vertebrae **L1-L3**.

Parts of Duodenum**I part (superior)**

- 5 cm long, most mobile part of duodenum
- On barium meal, I part is seen as '**duodenal cap**'.
- I part is MC site for duodenal ulcers; an ulcer on posterior wall of I part may erode the gastroduodenal artery leading to serious internal bleeding-hence called '**artery of duodenal hemorrhage**'!

II part (descending)

- 8 cm long.
- **Major duodenal papilla:** here the common bile duct and the main pancreatic duct of Wirsung form the hepato-pancreatic ampulla of Vater and open at its summit.
- **Minor duodenal papilla:** located 8 cm distal to pylorus but proximal to major duodenal papilla. The **accessory pancreatic duct** when present opens here.

Contd...

Contd...

III part (horizontal)

- 10 cm long; the III part is sandwiched between the **superior mesenteric artery in front** and the **abdominal aorta behind**.
- Lies against L3 vertebra transversely and more prone to trauma

IV part (ascending)

- 2.5 cm long

Blood Supply of the Duodenum

- The part of the duodenum *proximal to major duodenal papilla* develops from **foregut** and hence supplied by celiac trunk through **superior pancreaticoduodenal artery**, a branch of **gastrooduodenal artery**, which in turn is a branch of **common hepatic artery**.
- Part of duodenum distal to opening of major duodenal papilla is derived from the **midgut** and therefore supplied by **superior mesenteric artery** (through **inferior pancreaticoduodenal branch**).

Ligament of Trietz

- Ligament of Trietz (LoT) is a **fibromuscular** band, which suspends and supports the **duodea-jejunal flexure-suspensory muscle** of duodenum.
- It arises from the right crus of the diaphragm close to esophageal opening.
- Contains upper striated muscle (innervated by phrenic nerve) and lower smooth muscle (autonomic).
- It is an **important intestinal landmark** for ruling out intestinal malrotation in a child.
- Upper GI bleed - from *proximal* to LoT
- Lower GI bleed - from *distal* to LoT.

JEJUNUM AND ILEUM

Feature	Jejunum	Ileum
Location	Occupies left upper quadrant, 40% length	Occupies right lower quadrant, 60% length
Walls	Thicker and more vascular	Thinner and less vascular
Mesentery	Fat is minimum and appear as translucent windows near the vasa recta Only 2 series of arterial arcades	Fat present throughout mesentery and translucent windows are absent Several series of arterial arcades

Contd...

Contd...

Feature	Jejunum	Ileum
Circular mucosal folds (plicae circulares , or ' valves of Kerkring ')	Larger and closely set;	Smaller and sparse
Villi	Larger, thick (leaf like) and more numerous	Shorter, thinner (finger-like) and less abundant. (Absent over Peyer's patches)
Aggregated lymphatic follicles (Peyer's patches)	Smaller and few (almost absent)	Largest and most numerous
X-ray	Identified by valvulae conniventes	Described by Wangensteen as ' characterless '

Histology of Small Intestine

- Mucosa-simple columnar epithelium with microvilli
- Lamina propria contains **crypts of Lieberkuhn** which in turn contains **goblet cells**, **Paneth (zymogen) cells** and **neuroendocrine cells**.
- Submucosa contains **Brunner's glands**: that secretes alkaline mucus to neutralize acid contents entering the duodenum from the stomach; located **ONLY** in the **duodenal submucosa** (the only GI submucosal glands!!). In **peptic ulcer disease**, **hypertrophy of Brunner's glands** is seen.

EXTRA EDGE

- **Microfold (M) cells**: M cells are epithelial cells overlying lymphoid follicles in the intestinal wall. They take up antigens from the intestinal lumen by endocytosis and transport them to subadjacent lymphoid tissue, which can then produce antibodies against these antigens-thus they act as antigen **presenting cells**!

LARGE INTESTINE (COLON)

- 1.5 m long and consists of caecum, colon (ascending, transverse and descending colon), sigmoid colon, rectum and anal canal.
 - Cecum = 6 cm
 - Ascending colon = 15 cm
 - Transverse colon = 50 cm
 - Descending colon = 25 cm
 - Sigmoid colon = 40 cm
 - Rectum = 12-15 cm
 - Anal canal = 3.8 cm
- Types of cecum: **Ampullary** type is **MC (80%)**, appendix arises on medial side); others are **conical** type (appendix at tip) and **intermediate** type.

- Cecum has **NO** mesentery; widest diameter and most vulnerable to perforation
- **Shortest** part of colon = **Ascending** colon
- **Longest** part of colon = **Transverse** colon (50 cms).
- **Most mobile** part of colon = **Transverse** colon
- MC site of **volvulus** in colon = **Sigmoid** colon
- **Smallest diameter** in colon = **Sigmoid** colon
- **Retroperitoneal** parts: ascending colon, descending colon and rectum.

Special features of large intestine

- **Taeniae coli**: are **longitudinal muscle fibres** that are concentrated to form three ribbon-like bands, **start at the base of the appendix**. The 3 tinea coli are **tinea libera**, **tinea mesocolica** and **tinea omentalis**.
- **Haustrations**: Due to the taeniae being 'shorter' than the circular muscle coat, the intervening colonic wall is puckered and thrown into **sacculations** (haustrations)
- **Appendices epiploicae**: small peritoneum covered adipose projections found scattered over the free surface of the whole of colon (NOT found on cecum, appendix and rectum).

Blood Supply of Colon

- **Marginal artery of Drummond**-a paracolic anastomosis between colic branches of **superior mesenteric artery** (ileocolic, right colic, middle colic) and colic branches of **inferior mesenteric artery** (left colic and sigmoidal arteries).
- Watershed areas of the colon: areas of colon with poor blood supply resulting from incomplete anastomosis of marginal arteries. These include
- Splenic flexure (**Griffith point**)-watershed area between superior and inferior mesenteric artery
- Rectosigmoid junction (**Sudeck's point**)-Watershed zone between inferior mesenteric artery and internal iliac artery.

EXTRA EDGE

- **Caecum, prostate, pituitary**: Organs whose **breadth is more than length**
- Abnormal connective tissue band running across the ascending colon anteriorly = **Jackson veil**.
- The MC variant in blood supply of the colon is **absent right colic artery**.

VERMIFORM APPENDIX

- **Present only in humans**, certain anthropoid apes and the wombat.
- Length is 7.5 -10 cms; **MC position** of appendix is retrocecal; Least common is postileal

- It opens into the caecum 2 cm below the ileocecal orifice and "**valve of Gerlach**" guards this opening.
- **Appendicular A.** (an **end artery**) is a branch of **lower division of iliocolic A.** (branch of **superior mesenteric A.**)-remember that appendix also develops from the **midgut**.
- **Accessory appendicular A.** if present arises from **posterior caecal artery**.
- The submucosa of appendix contains a profusion of lymphoid follicles-hence called "**abdominal tonsil**".
- **McBurney's point** is at the junction of the **lateral 1/3 with medial 2/3** of a line joining the **anterior superior iliac spine and umbilicus**. Classically, it is the point of greatest tenderness in appendicitis.
- **Referred pain** is felt in the **T10 dermatome**-periumbilical.

MECKEL'S DIVERTICULUM

- **Meckel's diverticulum** is the **MC congenital abnormality** of the small intestine and GIT.
- Caused by an **incomplete obliteration of the vitelline duct** (i.e., **omphalomesenteric duct**)-i.e. it represents the patent intestinal end of the vitello- intestinal duct.
- It is typically lined by ileal mucosa, but **other tissue types are also found** with varying frequency, **ectopic gastric mucosa** in about 50%.
- A Meckel's diverticulum **possesses all 3 coats of the intestinal wall** and **has its own blood supply**. It is therefore **vulnerable to infection** and **obstruction** in the same way as the appendix
- Can also cause **intussusception, bleeding and volvulus**.
- Since both appendix and Meckel's diverticulum are derived from midgut - **BOTH** can present (when inflamed) with **peri-umbilical pain**.

Rule of 2s - Meckel's diverticulum

- It is present in about **2%** of subjects
- Its length is about **2 inches**
- Usually **2 feet (60 cm)** proximal to the ileocecal valve and occurs on the **antimesenteric** border of the ileum.
- **Present in 2%** of the population.

RECTUM

- The rectum measures approximately **12 cm** in length
- It is continuous with the sacrum at the **S3**, but **surgically the rectosigmoid junction lies opposite the sacral promontory**.

- The anorectal junction lies 2-3 cm in front of and slightly below the tip of the coccyx, here the **puborectalis** muscle encircles the posterior and lateral aspects of the junction creating the **anorectal angle** (normally 120 degrees).
- The rectum has **3 lateral curvatures**; the upper and lower, convex to the right; and the middle, convex to the left.
- Houston's valves**: On the mucosal (lumen) aspect these 3 curves are marked by semicircular folds called Houston's valves.
 - These valves **DO NOT** contain all muscle layers;
 - They are an excellent place to perform rectal biopsy since minimal risk of perforation
 - They are **NOT** present after mobilization of the rectum
 - Middle valve** corresponds to *anterior peritoneal reflection*.
- Ampulla**: The part of the rectum lying below the middle valve has a greater diameter than the upper third, and is known as ampulla of the rectum.
- The rectum is divided into 3 parts:
 - Upper third**: Which is *mobile and has a peritoneal coat*
 - Middle third**: *Peritoneum covers the only the anterior and part of the lateral surfaces*
 - Lowest third**: Lies deep in the pelvis surrounded by fatty mesorectum and has important relations to fascial layers.
- Lymphatic drainage is mainly upwards, along superior rectal vessels to superior rectal nodes (**pararectal lymph nodes of Gerota**).

Denonvillier's fascia (rectovesical fascia)

Separates the rectum from the prostate/vagina in front

Waldeyers fascia (Presacral fascia)

Separates the rectum from the coccyx and lower two sacral vertebrae behind

- Arterial supply**:
 - Superior rectal A.**: which is the *direct continuation of the inferior mesenteric artery*, is the main arterial supply.
 - Middle rectal A.**: Arising on each side from the internal iliac artery.
 - Inferior rectal artery**: terminal branch of internal pudendal artery
 - Median Sacral artery**: branch of abdominal aorta
- Venous drainage** is through superior rectal vein (drains into inferior mesenteric vein), middle rectal vein and median sacral vein.
- Nerve supply**

- Sympathetic supply-L1, L2
- Parasympathetic supply-S2, S3, S4
- Pain** impulses are carried by both sympathetic and parasympathetic nerves; whereas sensation of **distension** is carried through **parasympathetic** nerves.

EXTRA EDGE

- Structures felt on Per Rectal (PR) examination are**:
 - Anteriorly: Bulb/root of the penis, base of the bladder, seminal vesicle and rectovesical pouch (in males)
 - Anteriorly: Cervix, vagina and rectouterine pouch (of Douglas) in females
 - Laterally: ischioanal fossa, plevic, appendix (right side only), fallopian tubes and ovaries
 - Posteriorly: Sacrum, coccyx and anococcygeal body.

ANAL CANAL

- It is about **3.8 cm** long and is situated **below the pelvic diaphragm**
- The interior of anal canal is divided by pectinate line and Hilton's line into three parts
 - Upper part** (1.5 cm long)-**above** pectinate line
 - Middle part** (1.5 cm long)-called **pecten**
 - Lower part**-8-10 mm in length lined by true skin.
- Anal columns of Morgagni** are 6-10 vertical folds in the mucous membrane of **upper part** of anal canal. **Anal valves of Ball** are *transversely placed semilunar folds* linking the anal columns. **Anal sinus** is the space above each valve.
- The **pectinate line/dentate line** represents the **site of fusion of the proctodaeum and postallantoic gut**. Its significance is as in table below.
- Hilton's white line** corresponds to the intersphincteric groove and denotes the lower limit of the pecten.

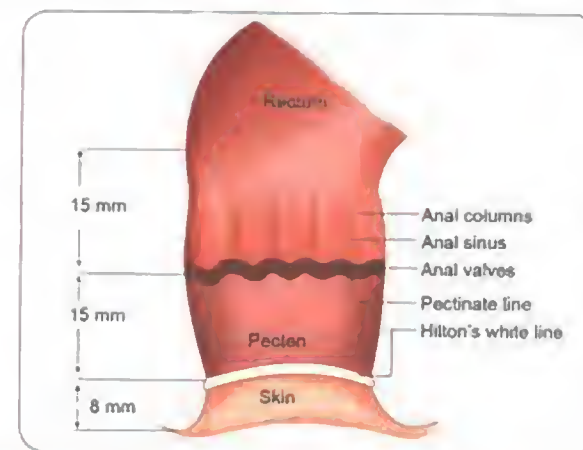
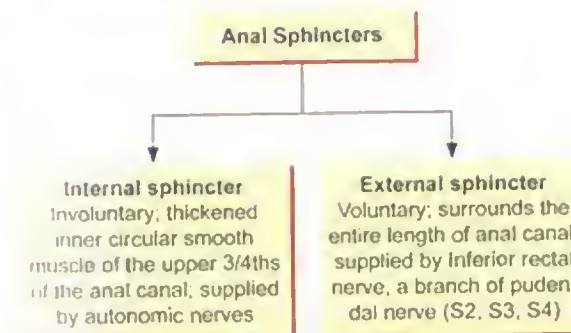


Fig. 2.62: Subdivisions and Internal features of anal canal

	Above pectinate line	Below pectinate line
Embryological origin	Endoderm (primitive rectum)	Ectoderm (proctodeum)
Epithellum	Simple Columnar	Nonkeratinised Stratified squamous
Artery	Superior rectal A. (terminal branch of inferior mesenteric A.)	Inferior rectal A. (branch of internal pudendal A.) + small contribution from median sacral artery
Vein	Superior rectal V. (portal venous system)	Inferior rectal V. (systemic venous system)
Lymph drainage	Internal iliac lymph nodes	Superficial inguinal lymph nodes
Nerves	Inferior hypogastric plexus - S2,3,4; autonomic nerves - insensitive	Inferior rectal N. - branch of pudendal N., somatic nerve - very sensitive-carries pain
Hemorrhoids	Internal hemorrhoids (not painful)	External hemorrhoids (painful)

Anal Sphincters



- External anal sphincter** has 3 parts:
 - Deep part** (rectal end) blends with **puborectalis** part of levator ani.
 - Middle Superficial part**: it is the **ONLY** part of the external sphincter having bony attachment-to the tip of the coccyx behind and to the perineal body in front; it does **NOT** completely encircle the anal canal; does **NOT** support the anal canal in the midline posteriorly.
 - Subcutaneous part**: encircles the lowest part of anal canal below the inter-sphincteric groove.
- Anorectal ring**: is formed by the **fusion of puborectalis, deep external sphincter and the internal sphincter**.

OTHER ABDOMINAL ORGANS

LIVER

Liver Basics

- Largest gland** and **heaviest organ** in the body (1.3-1.5 kgs).
- Liver is covered by a fibrous capsule - **Glisson's capsule**.

Anatomical Lobes of Liver

- Two lobes—Right and left lobes. As per this scheme, the caudate and quadrate lobes form part of the anatomic right lobe.
- Reidel's lobe** is a tongue shaped projection from the inferior border of Right lobe.
- Caudate lobe** is situated on the **posterior surface of the right lobe**; It is bounded on the right by groove for IVC, on left by fissure for ligamentum venosum and inferiorly by porta hepatis. Caudate lobe is unique because it is the **ONLY** part of the liver that is covered by the peritoneum of the lesser sac.

Functional Lobes of the Liver

- This is based on the area of drainage of bile by the right and left hepatic ducts.
- The line of demarcation passes through a plane connecting the gallbladder and inferior vena cava- **Cantle's line**-roughly falls along the **middle hepatic vein**.
- According to this subdivision, the quadrate lobe belongs to left lobe and caudate lobe belongs to both right and left lobes.

Couinaud's Segments

- 8 functional segments** of liver are present; each segment has **independent** artery, bile duct, tributary of hepatic vein and the portal tributary.
- Couinaud's Segment I** corresponds to **caudate lobe**, which is **unique** since it receives blood from right and left branches of hepatic artery and portal vein and it drains into both right and left biliary ducts and directly into the IVC.
- Couinaud's Segment IV** corresponds to **quadrate lobe**.

Blood Supply of the Liver

- Blood flow is at the rate of **1500 ml/min**.
- Of this **80%** of afferent blood supply is by **portal vein** and **25%** is conveyed by **hepatic artery**.
- Venous drainage is by the **hepatic vein into the IVC**.

Bare Area of the Liver

- A **triangular area devoid of peritoneal covering**, it is limited by the upper and lower layers of the coronary ligament and the triangular ligament
- It is situated on posterior surface of the **right lobe** and is in **contact with diaphragm**.
- This area is supplied by lower six intercostal nerves.
- **Clinically Important** because it **encloses the right extraperitoneal space**. It represents a site where infection can spread from the abdominal cavity to the thoracic cavity (as in amoebic hepatitis pus may spread into the pleural cavity).

Porta Hepatis

Porta hepatis contains

- Right and left hepatic ducts
- Right and left branches of hepatic artery
- Portal vein
- Hepatic lymph nodes

Histology of the Liver

- **Sinusoids of liver:**
 - Irregular "capillaries" with fenestrated endothelium (pores 100-200 nm in dia). NO basement membrane.
 - Allow macromolecules of plasma full access to basal surface of hepatocytes through **perisinusoidal space (Space of Disse)**.
- **Space of Disse** contains
 - **Ito cells (vitamin A synthesis)** and
 - **Kupffer cells (liver macrophages)**
- Apical surface of hepatocytes faces bile canaliculi; Basolateral surface faces sinusoids.

Subdivisions of Liver Parenchyma

- **Hepatic lobule:** is **hexagonal** in shape and forms structural unit of liver **around a central vein**.
- **Portal lobule:** **triangular** in shape and the **portal triad** is at its centre.
- **Portal acinus** (hepatic acinus) is a **diamond shaped** unit of liver parenchyma confined to two adjacent hepatic lobules. The portal acinus shows 3 zones depending on oxygen supply of the parenchyma
 - **Zone 1: Periportal zone** - has rich oxygen supply; affected 1st by viral hepatitis

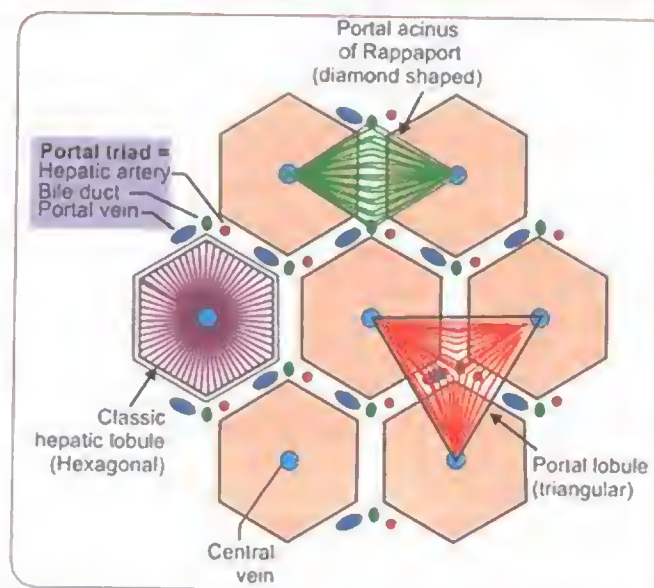


Fig. 2.63: Hexagonal hepatic lobule, triangular portal lobule and diamond-shaped portal acinus of Rappaport

- **Zone 2: Intermediate zone**
- **Zone 3: Pericentral vein (centrilobular) zone:** has poor oxygen supply; contains P 450 system, affected 1st by ischemia, most susceptible to toxic injury, alcoholic hepatitis.

BILIARY DUCT SYSTEM

Right and left hepatic ducts emerge from right and left lobe in porta hepatis

Unite to form **common hepatic duct**

Descends in **free edge of lesser omentum**

Joined by **cystic duct** to form **common bile duct (CBD)** (8 cm long and 6 mm diameter) that lies to the **right** of the **hepatic artery and portal vein**

CBD and main pancreatic duct join to form the **ampulla of Vater**, which opens into the **II part of duodenum** at the major duodenal papilla, which is surrounded by **sphincter of Oddi**.

EXTRA EDGE

- The right hepatic duct joins the left hepatic duct with a sharp curve; this is why **calculi are less commonly found in the right hepatic duct**.
- **Common bile duct** is **8 cm** long and descends in the **free margin of lesser omentum** and then passes **posterior to I part of duodenum**. It then passes **posterior to head of pancreas** and opens into the **II part of duodenum** (after joining pancreatic duct).

- **Sphincter of Oddi** is 10-15 mm in length situated within the muscular layer of the media of the duodenum. It has **3 distinct segments**: (1) **sphincter choledochus**, (3) **sphincter pancreaticus** and (4) **sphincter ampullae**. [BUT Gastroenterology books mention 4 sphincters by dividing one sphincter choledochus into two parts!! (superior and inferior)]
- **Van Meyenburg complexes:** Small clusters of dilated bile ducts in a fibrous stroma; an incidental portal tract lesion.

GALLBLADDER

- Pear shaped organ, 7.5-12.5 cm long.
- Average capacity is **50 ml**, but can **distend up to 50 times!**
- Adult Liver secretes 500 ml-1L of bile/day
- Bile is **concentrated upto 10 times** in gallbladder.
- Gallbladder has **neck, body and fundus**.
- **Hartmann's pouch:** Dilated area of the posteromedial wall of the neck of gallbladder; it is a **common site of stone impaction**.
- **Fundus** projects **beyond the inferior border** of the liver and comes in contact with anterior abdominal wall just below the right **ninth costal cartilage**.
- **Murphy's sign:** Pressure on the tip of right ninth costal cartilage (with patient sitting and with deep inspiration) causes sharp pain in **acute cholecystitis**.
- Gall bladder is supplied by **Cystic artery**-branch of the **right hepatic A.**; occasionally an **accessory cystic A.** arises from the **gastroduodenal A.**
- Nerve supply: sympathetic fibres from **celiac plexus** and parasympathetic fibres from **vagus**.
- **Cystic duct:** begins from neck of gallbladder, **3-4 cm long** and joins common hepatic duct to form common bile duct. Mucosal folds in **proximal portion** of cystic duct are called **valves of Heister**.

Calot's triangle

- **"Triangle" formed by the:**
 - **Cystic artery** superiorly
 - **Cystic duct** inferiorly, and
 - **Hepatic duct and common hepatic artery** medially
- **Cystic lymph node (of Lund)** lies in the angle between the cystic duct and hepatic duct.

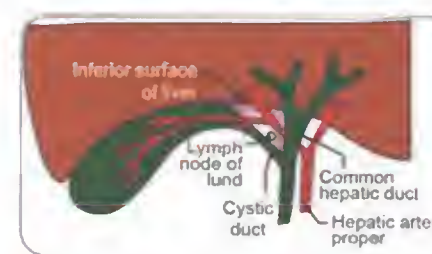


Fig. 2.64: Boundaries and contents of cystohepatic triangle of Calot

Other 'Eponymous' Gallbladder MCQ Points

- **Floating gallbladder:** has a mesentery
- **Sessile gallbladder:** cystic duct is absent and gallbladder opens directly into the bile duct
- **Phrygian cap:** seen radiologically on cholecystographies due to a constriction between the fundus and body (may be mistaken for a pathological deformity of the organ).
- **Rokitansky Aschoff sinuses:** Outpouchings of the mucosa of the gallbladder
- **Crypts of Luschka:** Are indentations of gallbladder mucosa that sink into the muscle coat.

EXTRA EDGE

- **Maynihan's hump:** The **right hepatic A.** is **tortuous** and cystic A. is short - this tortuosity of right hepatic A. is known as **'caterpillar turn'** or **'Maynihan's hump'**-most dangerous anomaly.
- **Pringle manoeuvre:** If bleeding persists during cholecystectomy, further control can be achieved by vascular inflow occlusion by placing an **atraumatic clamp across the foramen of Winslow** where it compresses the hepatic artery in the free margin of lesser omentum.

PANCREAS

- The pancreas is **12-15 cm long** and extends from duodenum to spleen and lies posterior to stomach.
- The pancreas is **retroperitoneal except** for its **tail** which lies in the **lienorenal ligament**.
- Parts of pancreas:
 - Head, Neck, Body and Tail.
 - **Uncinate process** is a projection arising from the lower part of the head.
 - **Tuber omentale:** A part of the body of the pancreas that projects upwards beyond the lesser curvature of the stomach and comes in contact with the lesser omentum

Relations of Pancreas

- Relations of **head** of pancreas
 - **Anteriorly:** I part of duodenum, transverse colon, coil of jejunum
 - **Posteriorly:** Common bile duct; IVC and termination of renal veins into it.
 - **Superiorly:** I part of duodenum
 - **Inferiorly:** III part of duodenum
- Relations of **uncinate process:**
 - **Anteriorly:** Superior mesenteric vessels
 - **Posteriorly:** abdominal aorta
- Relations of **neck** of pancreas
 - **Anteriorly:** gastroduodenal artery and pylorus of stomach

- **Posteriorly:** formation of portal vein by union of splenic and superior mesenteric veins.

Relations of body:

- **Posterior surface-** "**Bed of pancreas**" consists of splenic vein; abdominal aorta and origin of superior mesenteric artery; left renal vessels left kidney and left suprarenal gland; left crus of diaphragm.
- **Unique features of tail of the pancreas:**
 - **Most mobile part** of the pancreas.
 - Related to **lienorenal (splenorenal) ligament**.
 - Contains **maximum number of islets of Langerhans**.

Ducts of Pancreas

- **Duct of Wirsung:** Main duct of pancreas
- **Duct of Santorini:** Accessory pancreatic duct

EXTRA EDGE

- **Pancreatic divisum:** MC congenital anomaly of pancreas; ventral and dorsal buds fail to fuse with each other.

SPLEEN

- Galen called spleen as "**the organ full of mystery**"
- Spleen arises by mesenchymal differentiation along the left side of the **dorsal mesogastrium**.
- **Weight** of normal adult spleen in **75-150g**
- Spleen is situated in **left hypochondrium opposite the 9th-11th ribs**, posteriorly between the fundus of the stomach and the diaphragm in the **long axis of tenth rib**.
- The **spleen projects** into the **peritoneum of the greater sac**; hence it is lined everywhere with peritoneum of greater sac except at the hilum and pancreatic impression which are non-peritoneal.
- Spleen makes an angle of **45 degrees** with horizontal plane.
- **Accessory spleens** or **splenunculi** - MC are found near the **hilum of the spleen**.
- **Superior border** of spleen is **notched** at its lateral end:
 - This notching is evidence of fact that **spleen develops by fusion of multiple masses**
 - In an enlarged spleen, the notching is exaggerated.
- The **visceral surface** of spleen is **in contact with the adrenal gland** and upper pole of the **left kidney**, the **pancreas** and **splenic flexure of the colon**.
- **Splenic A.** - branch of celiac trunk (foregut A.) - supplies spleen.

Ligaments of Spleen

- The part of dorsal mesentery that extends b/n spleen and greater curvature of the stomach is called **Gastrosplenic ligament**.
- The part of dorsal mesentery that extends b/n spleen and left kidney is **splenorenal ligament**
- **Phrenocolic ligament:** connects left colic (splenic) flexure to diaphragm - **supports the anterior border of the spleen**.

Histology of Spleen

Red pulp

- Consist of splenic "sinuses" which are filled with blood separated by **splenic (Billroth) cords**.
- Sinusoids are lined by special banana shaped endothelial cells (**Stove cells**) which contain myofibrils that allow them to contract thereby opening up channels by which blood is discharged into the splenic substance
- "Marginal zone" bordering on white pulp
- Destruction of abnormally shaped and rigid red cells by **culling and pitting**

White pulp

- White pulp is made up of lymphoid follicles that are differentiated from lymphoid follicles elsewhere in body by presence of a **eccentrically situated arteriole**.
- "**PeriArterial Lymphoid Sheaths (PALS)**", rich in T-lymphocytes surrounds lymphocytes.
- On exposure to antigens, the lymphoid follicles become enlarged and are called **Malpighian corpuscles** (rich in B-lymphocytes).

Other Functions of Spleen are:

- Phagocytosis of foreign substances
- Platelet reservoir - spleen normally contains 30-40% of platelets.
- Erythrocyte production - upto 5th month of gestation.

Isomerism

Right Isomerism (asplenia syndrome)

- **Absence** of spleen
- **Double right sidedness** (patient appears to have two right sides) = **ivemark syndrome**.
- Both lungs have 3 lobes (**trilobed lungs**).
- Eparterial bronchi = main bronchus passes superior to ipsilateral main pulmonary artery.
- A/w bilateral right atria.

Left isomerism (Polysplenia syndrome)

- **Double left sidedness** (patient appears to have two left sides)
- Both lungs have 2 lobes
- A/w bilateral left atria

KIDNEYS

- Vertebral extent of the kidney is from **T12 to L3** vertebra.
- Kidney weight ranges from **130 to 170 grams**.
- **Right kidney** is at a **lower level** than the left, due to the liver in the right side.
- Kidneys are **retroperitoneal**.
- **Structures at the hilum of kidney** (from Anterior to posterior-VAP)
 - Renal Vein
 - Renal Artery
 - Renal Pelvis.
- **Renal angle:**
 - Is the angle between **lower border of the 12th rib** and **outer border of erector spinae**.
 - Renal pain is felt in the renal angle as a dull ache.

Coverings of the kidney

From inside to outside

- **Fibrous capsule (true capsule)** of collagen fibres easily stripped off in healthy kidney
- **Fatty capsule** (**Perirenal/perinephric fat**)
- **Renal fascia (false capsule or Fascia of Gerota)** forms a common covering to the kidney and suprarenal gland - further subdivided into **anterior fascia (Toldt)**; **posterior fascia (Zuckerkandl)**
- **Pararenal/paranephric fat**.

Posterior Relations of Kidney

- **Diaphragm** related to upper part
- **12th rib** related to right kidney and 11th and 12th ribs to left kidney
- From lateral to medial side - 3 muscles - **psoas major, quadratus lumborum and transversus abdominis**.
- **Subcostal nerve** and vessels, **iliohypogastric nerve** and **ilioinguinal nerve**.

Blood Supply of Kidneys

- **Renal A. from aorta** divides into **five vascular segmental arteries (end arteries)**.
- **Renal veins** drain into **IVC**.
- The **left renal V. receives the left testicular V. in the male** and this may get blocked by kidney tumor producing **left varicocele**.
- **Remember:**
 - **Right gonadal** (ovarian and testicular) and **right suprarenal veins** drain into **IVC**;

- **Left gonadal, left suprarenal and left inferior phrenic veins** drain into **left renal vein**.



Fig. 2.65: Clinical photo of left sided varicocele: 'bag of worms' look

Internal Structure of Kidney

- Outer **cortex**: consist of compactly packed nephrons and blood vessels.
- Inner **medulla**: consists of 6-12 pyramids; the apices of the pyramids, extend into minor calyces as renal papillae; the tip of each papilla is pierced by numerous apertures of **papillary ducts of Bellini**.

EXTRA EDGE

- **Morris parallelogram:** The outlines of both kidneys are mapped in the parallelograms that are drawn on the back.
- **Brodel's bloodless line:** Incisions are made along this line along the convex border of the kidney where territories of anterior and posterior branches of renal artery meet.
- **Left kidney** is usually chosen for **transplantation** because **it has longer renal vein**.
- Transplanted kidney is placed in the **right iliac fossa**, in the retroperitoneal region, leaving native kidney in situ.

URETER

- Develops from the **ureteric diverticula** arising from the **mesonephric duct**.
- **25 cm** in length; **3 mm** in diameter; it is **retroperitoneal**.
- During surgery, the ureter is recognised by its peristaltic movements.
- Pain of **ureteric colic** begins in the loin and shoots downwards and forwards to the groin, and the scrotum/labium majus.

Site of Constrictions of Ureter

- At the pelviureteric junction
- At pelvic brim (at level of bifurcation of common iliac artery and crossing of external iliac artery)
- Point of crossing of vas deferens in male or passing through broad ligament in female.
- At the point of entry into bladder wall-**vesicoureteric junction-narrowest part**.

Course of Ureter

- Ureter emerges from hilum of kidney and enters true pelvis by **crossing anterior to** bifurcation of **common iliac artery** and origin of **external iliac vessels** in front of **sacro-iliac joint**.
- Opposite the ischial spine, it turns **anteromedially** and reaches the bladder at **an angle**.

Relations of Abdominal Part of Ureter

Anterior relations of right ureter	Anterior relations of left ureter
Duodenum (III part)	Left colic vessels
Right colic vessels	Sigmoid vessels
Iliocolic vessels	Left gonadal vessels
Gonadal vessels	Sigmoid mesocolon
Root of mesentery	

- **Posterior relations on both sides**
 - Psoas major muscle, genitofemoral nerve and tips of lumbar transverse processes
 - Bifurcation of common iliac vessels at pelvic brim.

Relations of Pelvic Part of Ureter

- **Remember**—the structures passing **anterior to the pelvic part of ureter** are the **ductus deferens in the male** and the **uterine A. in the female**.

Blood Supply of Ureter

- Abdominal part: From **renal artery**, **gonadal artery** and abdominal **aorta**.
- Pelvic part: From **Inferior vesical artery** in male and **uterine artery** in female.
- At pelvic brim: From twigs of common and internal iliac arteries.

EXTRA EDGE

- Due to close relation of ureter to uterine artery ("water under the bridge"), the ureter is liable to injury during hysterectomy as it may be mistaken clamped along with uterine vessels.

- Steps to **prevent injury to ureter** during surgery are:
 - When in doubt stroke the ureter and wave of peristalsis is seen
 - During abdominal hysterectomy **intrafascial clamping of parametrium** also helps to prevent injury.

URINARY BLADDER

- The **mean capacity** of the bladder is about **220 ml**; sense of filling up of bladder occurs at about **100-150 ml**; **micturition** commonly takes place when the **bladder** contains about **280 ml**; at about **400 ml** pain and discomfort occurs.
- Empty bladder is tetrahedral in shape and has an apex; neck; four surfaces (posterior/base; superior surface; right and left inferolateral surfaces).

Relations of Bladder

- The apex is joined to umbilicus by the **median umbilical ligament** (remnant of the **urachus**).
- Base (posterior surface)
- In females, it is related to **cervix and vagina**
- In males, upper part of base is separated from rectum by **rectovesical pouch** and lower part is related to **seminal vesicles** and **ampulla of vas deferens**.
- Neck is most fixed part of bladder.
- The retropubic space/cave of Retzius separates the inferolateral surface from the pelvic surface of the pubis.

Ligaments of Bladder

- **True ligaments**
 - Median umbilical ligament
 - Medial and lateral puboprostatic (in male) or pubovesical (female)
 - Lateral true ligaments and posterior true ligaments are condensations of pelvic fascia
- **False ligaments**
 - Median umbilical fold
 - Medial umbilical fold (remnants of the **Obliterated umbilical arteries**)
 - Lateral false ligaments
 - Posterior false ligaments are sacrogenital folds

Interior of Bladder

- Internal trigone is on the **posterior surface/base** of the bladder; shaped like an **equilateral triangle**.
- Interureteric **ridge of Mercler** forms the base of the trigone.
- Distance between the ureteric orifices is **2.5 cm** in empty bladder (5 cm in distended bladder).

- Unlike mucosa of rest of bladder which develops from endoderm; **mucosa of trigone develops from mesoderm**; this mucosa is smooth and firmly adherent.
- In the male, the internal urethral orifice is guarded by an elevation of the trigone called **uvula vesicae** produced by projection of **median lobe of prostate**.
- Just beneath the mucosa of trigone, there is a layer of smooth muscle (trigonal muscle of Bell).

Blood and nerve supply of bladder

- **Blood supply** is from the **superior and inferior vesical arteries** in males; in females from **superior vesical and vaginal artery**.
- **Parasympathetic supply** is from **nervi erigentes (S2, 3, 4)**. These fibres pass through **pelvic splanchnic nerves** → **inferior hypogastric plexus** → **vesical plexus**. It is motor to detrusor muscle but inhibitor to sphincter vesicae.
- **Sympathetic fibres (T11 to L2)** are inhibitory to detrusor and motor to sphincter vesicae.

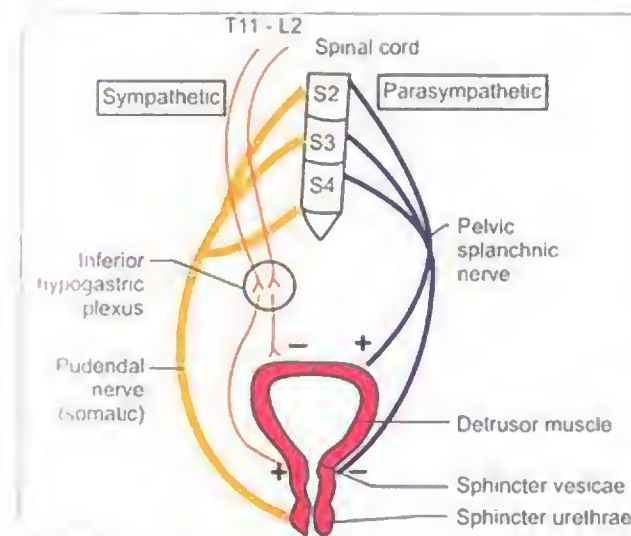


Fig. 2.66: Nerve supply of urinary bladder, sphincter vesicae and sphincter urethrae

MALE URETHRA

- **20 cm long**, consists of 3 parts as below.
- The **epithelium lining the urethra (transitional epithelium)** is continuous with the epithelial lining of the bladder – also see table below regarding epithelial lining of various parts of male urethra.
- **Lacuna magna (of Guerin)** is situated on the **roof of navicular fossa**.
- The **external urethral orifice is the narrowest part** of the urethra.

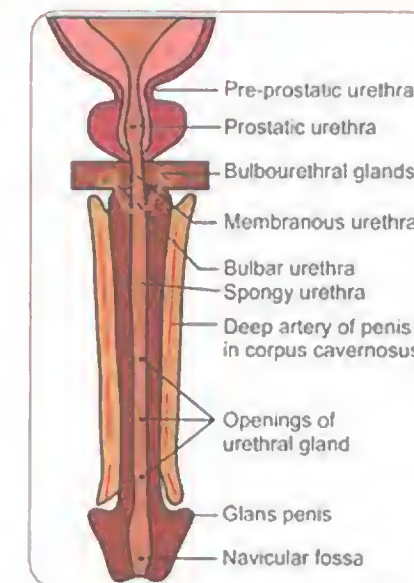


Fig. 2.67: Gross anatomy of male urethra

Prostatic urethra

- 3 cm
- Widest and most dilatable
- **Horse-shoe** shaped in cross section
- Posterior wall has linear bulge – **urethral crest** the widest part of which is the **colliculus seminalis** or **verumontanum**.
- **Prostatic utricle** opens into the urethral crest
- Ejaculatory ducts open just lateral to the prostatic utricle
- **Prostatic sinus** is a groove on each side of the urethral crest into which the prostatic ductules open.

Membranous urethra

- 2 cm
- **Shortest and least dilatable**.
- **Star** shaped in cross section
- Surrounded by fibres of **sphincter urethrae** (external sphincter).
- Bulbourethral glands of **Cowper (BUGC)** are placed one on each side of the membranous urethra.

Penile (spongiosae, cavernous) urethra

- **15 cm; longest** part of urethra
- Contained in the corpus spongiosum
- **Trapezoid** in cross section
- It contains 2 dilatations
 - Intrabulbar fossa in the beginning, and navicular fossa in the glans penis.
- **BUGC** and **Glands of Littre** open into penile urethra in **intrabulbar fossa**.

Epithelial Lining of Male Urethra

Urethral part	Lining epithelium
Preprostatic and proximal prostatic urethra	Urothelium (transitional epithelium) of bladder

Contd...

Contd...

Urethral part	Lining epithelium
Below the ejaculatory ducts Membranous urethra Proximal penile urethra	(Pseudo) Stratified columnar epithelium
Distal penile urethra	Stratified squamous epithelium

FEMALE URETHRA

- 4 cm long, corresponds to the **upper part of prostatic urethra** of male.
- It is embedded in the anterior wall of the vagina; the inner mucosal layer is continuous with that of the bladder.
- Lined by **transitional epithelium**.

MALE REPRODUCTIVE ORGANS**PENIS**

- Penis has a **body and root**.
- Body of penis consist of **2 Corpora cavernosa** (2" C's!) and **1 median corpus spongiosum**. *Corpus spongiosum* expands at its distal end to form the **glans penis**.
- *Corpora cavernosa* are enveloped by **tunica albuginea**.
- Superficial fascia of the penis differentiates into an outer **loose areolar tissue** and an inner well defined membrane known as **Buck's fascia**.
- **Buck's fascia (deep fascia of penis)**, surrounds the three corpora but does not extend onto the glans.

Nerve supply of penis

- Skin of penis-by pudendal nerve via dorsal nerve of penis and posterior scrotal nerve
- A small area on dorsum of root is supplied by ilioinguinal nerve.
- **Erection of penis (Pointing!)**: Vascular phenomenon; Parasympathetic-Nervi erigentes, (S2, 3, 4); ("S2,3,4 keeps your penis off the floor!")
- **Ejaculation (Shooting!)**: Sympathetic control (contraction of vas deferens; prostate) and is derived from **L1** segment via superior and inferior hypogastric plexus.
- Mnemonic: "Point and Shoot!"

Arterial supply of penis:

- (1) **Internal pudendal artery-main artery** (through its 3 branches-deep artery of penis; dorsal artery of penis and artery of bulb of penis)
- (2) **femoral artery** (through superficial external pudendal artery)

- The collection of urethral glands in the mucosa, one on each side of the urethra are called **paraurethral glands of Skene** (homologous of the male prostate).
- There is **no internal urethral sphincter** in female urethra.

URETHRAL SPHINCTERS

Internal urethral sphincter (sphincter vesicae)	External urethral sphincter (sphincter urethrae)
<ul style="list-style-type: none"> • Involuntary • Nonstriated muscle (smooth). • Surrounds neck of Urinary Bladder. • S/b vesical plexus (sympathetic). 	<ul style="list-style-type: none"> • Voluntary • Striated muscle • Surrounds membranous urethra • S/b perineal branch of pudendal nerve (S2, 3, 4) (parasympathetic). • Origin is from ischiopubic rami on each side

- **Helicine arteries of penis** are five branches of cavernosal artery (deep artery of penis) that fill sinusoidal space of corpora cavernosa.
- **Lymphatics** from **glans penis** drain into **deep inguinal nodes**; from rest of penis into superficial inguinal nodes.

EXTRA EDGE

- In anterior urethral injury:
 - If Buck's fascia intact blood & urine remain within the penis '**sleeve hematoma**'
 - If Buck's fascia disrupted blood & urine can spread to the scrotum, abdominal wall, perineum and thigh. Extravasation into the superficial perineal pouch '**butterfly hematoma**'.

Hypospadias

- It is seen in **1:300 boys**, the urethra opens **proximally and ventrally (inferiorly)**.
- MC, the **opening is just proximal to the glans**
- It is attributed to **failure of complete urethral tubularisation** in the fetus; the foreskin is deficient ventrally and there is a variable degree of **chordee** (a ventral curvature of the penis most apparent on erection)
- Ritual **circumcision** is **contraindicated** in infants with hypospadias because the **foreskin is often required for the reconstruction**.

Epispadias

- Penile urethra opens on superior (dorsal) side of penis - due to faulty positioning of genital tubercle
- A/w exstrophy of bladder.

SCROTUM

- The **left half of scrotum** is slightly lower due to the greater length of left spermatic cord.
- The scrotal temperature is lower than body temperature by about **3 degrees centigrade**.
- Lymphatics from scrotal skin drain to **superficial inguinal nodes**.
- **Anterior 1/3** of scrotal skin supplied by **ilioinguinal nerve** and **genital branch of genitofemoral nerve** (L1).
- **Posterior 2/3** of scrotal skin supplied by **posterior scrotal nerves** and perineal branch of **posterior cutaneous nerve of thigh** (S3).
- Layers of the **scrotum** from within outwards:
 - Skin
 - **Dartos muscle** (supplied by **sympathetic nerve**)
 - **External spermatic fascia** (extension from external oblique)
 - **Cremasteric fascia** (continuous with fascia from internal oblique)
 - **Internal spermatic fascia** (from **fascia transversalis**).

EXTRA EDGE

- MC cause of scrotal swelling is **hydrocele**-collection of fluid in tunica vaginalis of testis. In draining of hydrocele all the above layers are pierced and also the parietal layer of **tunica vaginalis**.

TESTIS

- Volume of testis **before puberty** = **0.75-2 ml**; volume of **adult testis** = **15-20 ml**.
- Left testis slightly lower than the right (since **left spermatic cord** is longer).
- There is a small oval body attached to upper pole of the testis called **appendix of testis** which is a **remnant of paramesonephric duct**.
- **Inferior pole** of testis is attached to scrotal wall by **scrotal ligament** which is remnant of **gubernaculum testis**.
- The **epididymis** is attached to its **posterolateral surface**.
- Coverings of testis (from outside to inside)
 - **Tunica vaginalis**-a serous sac.
 - **Tunica albuginea** is thick **fibrous** covering of the testes.
 - **Tunica vasculosa**
- Testis consists of 200-300 lobules; each lobule consisting of 2-3 **seminiferous tubules** (where spermatozoa are formed). Seminiferous tubules join at the apex of the lobules to form **straight tubules** which anastomose with each other to form **rete testes**, which emerge from upper pole and enter the epididymis.
- **Sertoli cells** (sustentacular cells) are the **only** non-germinal individuals in the cells of the seminiferous tubules. They provide the germ cells with **nutrition**;

secretes fluid that helps spermatozoa move along the seminiferous tubules. This fluid is rich in **testosterone**.

Blood-Testis barrier

- The tight junctions between the **Sertoli cells** forms the blood testis barrier.
- This barrier maintains germ cells in an **immunologically privileged** location (within seminiferous tubules) and limits the transport of many substances from the blood to seminiferous tubules' lumen.

- **Interstitial cells of Leydig** are **epithelioid** cells that secrete **androgens** (testosterone)
- Testis is supplied by **testicular artery**, a **branch of abdominal aorta** at L2 level.
- The veins emerging from testes and epididymis form the **pampiniform plexus**. Ultimately one vein is formed and **right testicular vein** drains into **IVC** and **left testicular vein** drains into **left renal vein**.
- Lymphatics from testis drain into **para-aortic nodes**.

EXTRA EDGE

Immune privileged sites in the body are:

- Testis (seminiferous tubules)
- Anterior chamber of the eye
- Placenta and fetus
- Brain

EPIDIDYMIS

- Epididymis is a mass of **highly coiled tubules** that act as **reservoir of spermatozoa**.
- Upper end of epididymis is the **head**; middle part is **body** and lower part the **tail**.
- The body and tail are made of a single duct, the **duct of epididymis** which is highly coiled on itself. At the lower end of the tail, the duct becomes continuous with the **ductus (vas) deferens**.
- **Sperms** attain **motility** in the **epididymis**.
- **Epididymis** is supplied by **testicular artery**.

DUCTUS (VAS) DEFERENS

- It is a thick walled muscular tube 45 cm long.
- It has narrow lumen, except at the terminal dilated part called the **ampulla**.
- It **enters the spermatic cord** and **passes through the inguinal canal**.
- At the deep inguinal ring, it leaves the spermatic cord and hooks around the **lateral side of inferior epigastric artery**.
- In the region of ischial spine, it **crosses the ureter** and then bends medially to reach the base of the bladder.

- There is **no intervening peritoneum** between the bladder base and the ductus deferens.
- At the base of the prostate it is joined by the **duct of seminal vesicle** to form the **ejaculatory duct**.
- Ductus deferens is supplied by **artery to ductus deferens**, a branch of **superior vesical artery** (rarely may arise from **inferior vesical artery**).

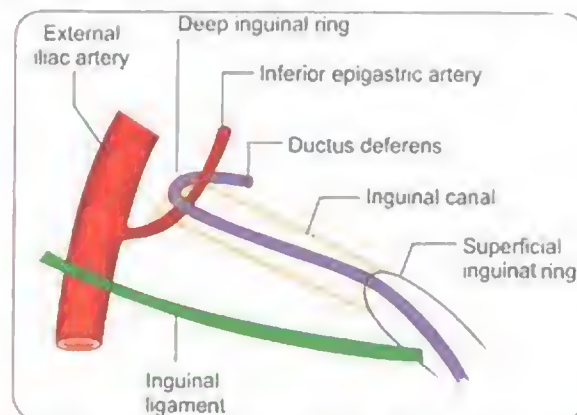


Fig. 2.68: Scheme to show relationship of ductus deferens to inferior epigastric artery also note relationship of the artery to the deep inguinal ring

PROSTATE

- Prostate gland develops from the primitive urethra as a series of solid epithelial buds (i.e. from the **caudal part of the vesicourethral canal**, and from the **pelvic part of definitive urogenital sinus**).
- There are 5 lobes in the prostate:
 - 1 anterior lobe
 - 2 lateral lobes
 - 1 **Posterior lobe** (MC site of **primary Carcinoma**).
 - 1 **Median lobe** (MC site of **Benign Hypertrophy prostate-BPH**)
 - "Priyanka Chopra Mein Baat Hain!")
- **Corpora amylacea** are found within the lumen of prostatic follicles.
- Prostatic venous plexus has a valveless communication with vertebral venous plexus (**Batson's plexus**) through which prostatic cancer can spread to vertebrae.

Note

- Spermatic cord is discussed under hernia topic in surgery.
- Female reproductive organs discussed under gynecology chapter (Pg 997).

PERINEUM

PERINEUM

- It is a **diamond-shaped** area bounded by two ischial tuberosities on each side, upper part of pubic arch anteriorly and tip of coccyx posteriorly.
- A transverse line joining the anterior parts of the ischial tuberosities divides the perineum into an **anal triangle** (contains anal canal) and **urogenital triangle** (contains external genitalia).
- **Urogenital triangle** is divided into **superficial** and **deep perineal pouch** described below.
- Deep fascia of the perineum is the **Gallaudet's fascia**.

Superficial Perineal Pouch

- This is a potential space that lies beneath the skin of the perineum. It is the Space between the membranous layer of superficial fascia (**Colle's fascia**) and the inferior fascia of the urogenital diaphragm
- Its contents in males and females are as in below table:

Males	Females
Penile (spongy) urethra	Urethra Vestibule of vagina
Muscles: bulbospongiosus, ischiocavernosus and superficial transverse perineal muscle	Muscles: bulbospongiosus, ischiocavernosus and superficial transverse perineal muscle

Contd...

Contd...

Males	Females
Branches of internal pudendal artery: Perineal artery (posterior scrotal artery; dorsal artery of penis and deep artery of penis)	Branches of internal pudendal artery: Perineal artery (posterior scrotal artery; dorsal artery of clitoris and deep artery of clitoris)
Branches of pudendal nerve: Perineal nerve (posterior scrotal nerves); dorsal nerve of the penis	Branches of pudendal nerve: Perineal nerve (posterior labial nerves); dorsal nerve of the clitoris
Bulb of the penis Crura of the penis	Vestibular bulb Crura of clitoris
Perineal body	Perineal body Round ligament of the uterus
Duct of bulbourethral gland	Greater vestibular glands of Bartholin

Deep Perineal Pouch

- This is a closed potential space that lies **between the superior and inferior fasciae of the urogenital diaphragm**.
- Its contents in males and females are as in below table

Males	Females
Membranous urethra	Urethra and vagina

Contd...

Contd...

Males	Females
Deep transverse perineal muscle and sphincter urethrae muscle	Deep transverse perineal muscle and sphincter urethrae muscle
Bulbourethral glands of Cowper	No glands
Branches of the internal pudendal artery (artery to penis)	Branches of the internal pudendal artery (artery to clitoris)
Branches of the pudendal nerve (dorsal nerve of penis)	Branches of the pudendal nerve (dorsal nerve of clitoris)

Ischiorectal Fossa

- **Anal triangle** is the posterior subdivision of the perineum and is traversed by anal canal in center and is supported on either side by fat filled **ischioirectal fossa** (a.k.a ischioanal space).
- Boundaries
 - **Anteriorly:** Posterior margin of perineal pouches
 - **Posteriorly:** sacrotuberous ligament and lower margin of gluteus maximus.
 - **Laterally:** Ischial tuberosity and obturator internus
 - **Medially:** Sphincter ani externus and levator ani.
 - **Base/Floor:** perineal skin
 - **Apex:** Line where the obturator fascia meets the inferior fascia of pelvic diaphragm (anal fascia)
- **Pudendal canal (Alcock's canal)** – is a fascial tunnel in the lateral wall of the ischioirectal fossa containing **pudendal nerve and internal pudendal vessels**

Urogenital Diaphragm

- It is formed by the **sphincter urethrae** and the **deep transverse perineal muscles** (a.k.a **transversus perinei profundus**).

Perineal Body

- A fibromuscular node located between the anal canal and lower part of posterior vaginal wall. A.k.a **centre point of the perineum**.

- It gives attachment to following muscles:

- Paired (right and left):
- Superficial transverse perinei
- Deep transverse perinei
- Bulbospongiosus
- Pubovaginalis part of levator ani
- Unpaired: Sphincter urethrae
- Sphincter ani externus.

PUDENDAL NERVE

- Pudendal nerve is the **chief nerve** of **perineum** and **external genitalia**
- It is a **mixed nerve** (motor + sensory)
- It arises from **sacral plexus** from **ventral rami** of **S2,S3,S4**.
- It originates in the pelvis, enters gluteal region through **greater sciatic notch**, leaves it through **lesser sciatic notch** to enter the pudendal canal.
- Branches of pudendal nerve
 - **Inferior rectal nerve** (given off in pudendal canal)
 - **Perineal nerve** (larger terminal branch of pudendal nerve)-gives off two **posterior scrotal/labial nerves** and **muscular branches**.
 - **Dorsal nerve of the penis/clitoris** (smaller terminal branch of pudendal nerve).

PELVIC DIAPHRAGM

- **Levator ani and coccygeus** muscles may be regarded as one morphological entity and the muscle with its fascial covering is called **pelvic diaphragm**.
- This diaphragm separates pelvis from the perineum.
- **Levator ani** is divisible into **pubococcygeus; iliococcygeus; ischiococcygeus**.
- Middle fibres of the **pubococcygeus** form **puborectalis**, mainly responsible for **fecal continence**.
- Pelvic diaphragm is pierced by the urethra and anal canal (also by vagina in female).

BLOOD VESSELS OF THE THORAX AND ABDOMEN

AORTA

Parts of Aorta

- Ascending aorta
- Arch of aorta
- Descending/Thoracic aorta
- Abdominal aorta

Branches of Ascending Aorta

- Left and Right Coronary Arteries

Branches of Arch of Aorta

- Left Common Carotid A.
- Left subclavian A.
- Brachiocephalic A.

- Right Common Carotid A.
- Right Subclavian A.

Branches of Descending/Thoracic Aorta

- Visceral:
 - Pericardial A.;
 - Oesophageal artery (4 to 5 in number);
 - Bronchial A. (one on right side and 2 on left side)
 - Mediastinal A
- Superior Phrenic A. or Phrenic A.
- Posterior intercostal A. of 3rd to 11th spaces-9 pairs

Branches of Abdominal Aorta

- | | |
|-------------------------|---|
| Dorsal branches | <ul style="list-style-type: none"> • Lumbar A.-4 pairs • Median Sacral A.-single |
| Lateral branches | <ul style="list-style-type: none"> • Inferior Phrenic A. • Middle Suprarenal A. • Renal A. • Testicular/Ovarian A. • Common iliac A. |
| Ventral branches | <ul style="list-style-type: none"> • Celiac A. • Superior Mesenteric A. • Inferior Mesenteric A. |

Further Course of Abdominal Aorta

- The abdominal aorta divides at the left side of the body of the L4 vertebra into **right and left common iliac A.**
- Each common iliac A. in turn divides into **external and internal iliac A.**, anterior to the sacroiliac joint.

MORE ABOUT THE BRANCHES OF AORTA

- Each Common carotid A.: divides into **Internal and External Carotid A.** Branches of these have been mentioned under "Blood supply of the brain".
- Each Subclavian A. is divided into three parts by **Scalaneus anticus** muscle.

Branches of Subclavian Artery

- | | |
|-------------------------------|--|
| Branches from I part | <ul style="list-style-type: none"> • Vertebral A. • Internal thoracic A. • Thyrocervical trunk • Inferior thyroid A. • Suprascapular A. • Superficial Cervical A. • Costocervical trunk (on left side) • Superior Intercostal A. • Deep Cervical A. |
| Branches from II Part | <ul style="list-style-type: none"> • No branch on left side • Gives Costocervical trunk on right side. |
| Branches from III part | <ul style="list-style-type: none"> • Dorsal scapular A. |

- Subclavian A. continues downward as the **Axillary A.** Axillary artery has been covered under "Axilla" in the section on **upper limb**. Further continuation of axillary artery as brachial artery and its branches-radial and ulnar is covered under "Upper limb" section under "Blood supply of Upper Limb".

Branches of Celiac Artery are:

- **Common Hepatic A.:** gives rise to:
 - Right gastric A.
 - Cystic A.
 - Right and Left hepatic branches
 - Gastroduodenal A. which intum gives:
 - Right gastroepiploic A.;
 - Superior Pancreaticoduodenal A.
 - Supraduodenal artery.
- **Left Gastric A.:** **Smallest** branch of Celiac A. It runs along the lesser curvature of the stomach. It gives few oesophageal branches also.
- **Splenic A.:** **Largest** branch of celiac A., is an end artery. Its branches are:
 - Left gastroepiploic A.
 - Short gastric branches (*run in gastrosplenic ligament*)
 - Posterior gastric artery (*rarely*)
 - Pancreatic branches

Branches of superior mesenteric A.

- It supplies all the derivatives of the midgut from distal to the major duodenal papilla to the right two thirds of the transverse colon and lower half of the pancreas.

Branches of inferior mesenteric A.

- Left Colic A.
- Sigmoid A.
- Superior rectal A.

EXTRA EDGE

- **Arc of Rialan:** It is an inconstant artery that connects the **proximal superior mesenteric artery (middle colic branch of the SMA)** to the **proximal inferior mesenteric artery (left colic branch of the IMA)**, a.k.a, the **mesenteric meandering artery (of Maskowitz)** or **central anastomotic mesenteric artery**.
- Collateral vessels within the colon meet at the **splenic flexure** and **descending/sigmoid colon**. These areas, which are **inherently at risk for decreased blood flow**, are known as **Griffiths' point** and **Sudeck's point**.
- The MC variant in blood supply of the colon is **absent right colic artery**.

Branches of Internal Iliac Artery

Posterior Division

- Iliolumbar artery
- Lateral sacral arteries (2 on each side)
- Superior Gluteal artery (largest)

Anterior Division

- Inferior gluteal A.
- Internal Pudendal A.
- Inferior vesical A (corresponds to *Vaginal A* in females)
- Middle rectal A
- Obturator A.
- Superior vesical A (gives artery to vas deferens)
- Uterine A (in females only)

Mnemonic: "I (Iliolumbar) Love (Lateral sacral) Going (Gluteal-superior and inferior) Places (Pudendal, internal) In (Inferior vesical) My (Middle rectal) Own (Obturator) Sexy (Superior vesical) Underwear (Uterine)"; the first three are branches of posterior division and rest are from anterior division.

EXTRA EDGE

- In 20%, the obturator artery may be replaced by a large pubic branch from the **inferior epigastric artery** instead of the internal iliac artery-this is the **accessory (abnormal) obturator artery**. This artery is closely related to femoral ring-either it passes lateral to femoral ring (safe position) or it passes **medial to femoral ring in close relation to lacunar ligament (unsafe position)**-this unsafe artery is prone to injury when lacunar ligament is cut to relieve femoral hernia.
- Presence of anastomoses between the normal and accessory obturator artery may lead to significant hemorrhage during groin surgery and pelvic injury-hence called "**corona martis**" (*crown of death*).

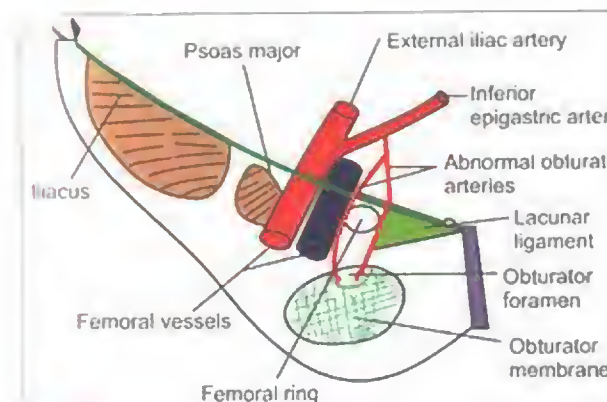


Fig. 2.69: Abnormal obturator artery and its relations to femoral ring (when the artery is laterally related to femoral ring, it is safe. When it is in medial relation to femoral ring, it is unsafe)

Branches of External Iliac Artery

- Inferior epigastric
- Deep circumflex iliac
- Branches to psoas major

External Iliac artery continues downwards as the femoral artery and thence downwards as the popliteal and tibial arteries-covered under "Lower limb" under "Blood supply of Lower limb".

Internal Pudendal Artery

- It is a **branch of anterior division of internal iliac artery**; it is **larger in males**.
- It is accompanied by pudendal nerve and has same course as pudendal nerve.
- Branches are:
 - **Inferior rectal artery**
 - **Perineal artery**-gives off **posterior scrotal/labial artery** and **transverse perineal branch**
 - **Artery to bulb** of penis/clitoris-which gives off these branches
 - Artery to bulb
 - Urethral artery
 - Deep artery of penis/clitoris
 - Dorsal artery of penis/clitoris.

MAIN VEINS OF THE THORAX AND ABDOMEN

External Jugular Vein

- It is formed just **behind the angle of the mandible** by the union of the posterior division of the **retromandibular vein** with the **posterior auricular vein**.
- It terminates by opening into the **subclavian vein**.

Internal Jugular Vein

- It begins as a continuation of the **sigmoid sinus** at the jugular foramen and terminates at root of neck by **joining the subclavian vein** to form the **brachiocephalic vein**.
- Branches are: (From inferior to superior)
 - **Middle Thyroid Vein**
 - **Superior Thyroid Vein**
 - **Lingual Vein**
 - **Common Facial vein**
 - **Pharyngeal vein**
 - **Inferior Petrosal sinus**
 - **Mnemonic:** "**M**edical **S**chools **L**et **C**onfident **P**eople **I**n!"

Brachiocephalic Veins (BV)

- Each (right and left) brachiocephalic vein (BV) is formed **behind the respective sternoclavicular joint** by **union of IJV and subclavian veins**.

- Both veins have NO valves.
- Right BV** is short (2.5 cm); its tributaries are:
 - Right vertebral vein;
 - Right internal thoracic vein;
 - Right inferior thyroid vein and
 - First right posterior intercostal vein.
- Left BV** is 6 cm long; its tributaries are:
 - Left vertebral vein;
 - Left internal thoracic vein;
 - Left inferior thyroid vein and
 - First left posterior intercostal vein
 - Left superior intercostal vein
 - Thymic and pericardial veins

Azygos Vein

- The name azygos vein means 'single/unpaired' or 'without companion'.
- Azygos vein is present on **right side only**; it HAS valves.
- It begins on posterior abdominal wall usually as a continuation of lumbar azygos vein (which arises from posterior aspect of IVC) or is formed by the union of right ascending lumbar and right subcostal veins.
- It enters the posterior mediastinum through the aortic opening of the diaphragm.
- It drains into the posterior aspect of SVC.
- Tributaries:
 - Right superior intercostal vein
 - Right posterior intercostal vein from fourth space downwards
 - Right subcostal vein
 - Right ascending lumbar vein
 - Hemiazygos vein
 - Accessory hemiazygos vein (superior hemiazygos vein)
 - Right bronchial vein
 - Esophageal vein
 - Pericardial Vein
 - Mediastinal Veins.

Hemiazygos Vein

- Present on **left side**
- It is formed as a continuation of lumbar azygos vein (which arises from posterior aspect of IVC) or is formed by the union of left ascending lumbar and left subcostal veins.
- Hemiazygos vein pierces the left crus of the diaphragm and enters the posterior mediastinum.
- Its tributaries are:
 - Left ascending lumbar vein

Left subcostal vein

- Left posterior intercostal veins of 9th to 11th intercostal spaces.

Accessory hemiazygos vein

- A.k.a **superior azygos vein**
- Begins as a continuation of the fifth posterior intercostal vein and descends on left side of the vertebral column. At the level of T7 vertebra it crosses over to right side behind the descending aorta and thoracic duct to open into the azygos vein.
- Its tributaries are:
 - 5th to 7th left posterior intercostal veins
 - Left bronchial vein.

Superior Vena Cava

- SVC is formed by junction of right and left brachiocephalic veins and has NO valves; 7 cm long.
- Azygos vein is the only major tributary.
- Remember 1, 2, 3-SVC** is formed at level of 1st costal cartilage, is joined by azygos vein at the level of 2nd costal cartilage and opens into the right atrium at the level of 3rd costal cartilage.

Inferior Vena Cava

- It is formed the union of the right and left common iliac veins anterior to the body of the L5 vertebra (a little to the right) and has NO valves.
- Its tributaries are:
 - Hepatic veins (right, middle and left)
 - Right suprarenal vein
 - Renal veins
 - Right gonadal vein (testicular or ovarian)
 - Inferior phrenic vein
 - Third and fourth lumbar veins directly open into the IVC (1st and 2nd lumbar veins open in the ascending lumbar vein or lumbar azygos vein)

Portal Vein

- Is about 8 cm long and starts at the level of the L2 vertebra and is formed by the junction of the superior mesenteric and splenic vein, in front of the IVC and behind the neck of the pancreas.
- It is related anteriorly to first part of duodenum and to its right lies the common bile duct.
- Normal portal vein pressure** is about 5-10 mmHg (10-15 mm saline).

Sites of Portal Systemic Anastomoses

Site of anastomosis	Clinical sign	Portal → systemic
Lower end of esophagus	Esophageal varices	Left gastric → esophageal
Umbilicus	Caput medusae	Paraumbilical → superficial and inferior epigastric
Anal canal wall	Hemorrhoids	Superior rectal → middle and inferior rectal
Nare area of liver (porto-caval)		Hepatic venules → phrenic and intercostal veins
Posterior abdominal wall		Veins of retroperitoneal organs → renal veins
Intrahepatic		

Vessels Preferred for Procedures

Coronary artery bypass grafting (CABG)	Internal mammary A.
Coronary angiography/ cardiac catheterization	Femoral A. (Seldinger technique)
Arteries favorable for cannulation	Radial A. and Posterior tibial A.
Injecting dye in Fluorescein angiography	Antecubital vein

Central Venous line placement

Insertion of pacemaker wires

Right Subclavian vein

Subclavian vein

Sources of Bleeding

In Extradural hemorrhage	Middle meningeal A.
In Subdural hemorrhage	Bridging veins
In hemoptysis and bronchiectasis	Bronchial A.
In blunt eye injury (ball, shuttlecock)	Circulus iridis major
In Duodenal Ulcer	Gastroduodenal A.
In retropubic prostatectomy	Dorsal venous plexus
In menstruation	Spiral arteries
In hysterectomy	Internal Iliac A.

Origin of Nutrient Arteries

Femur	2nd Perforating branch of Profunda femoris A
Tibia	Posterior tibial A (gives largest nutrient A in body to Tibia)
Fibula	Peroneal A
Humerus	Brachial and Profunda Brachii arteries

HEAD AND NECK

BONES AND JOINTS OF HEAD AND NECK

SKULL

Skull Bones

Bones of cranium/ calvarium (8)		Bones of Face (14)	
Paired	Unpaired	Paired	Unpaired
Parietal	Frontal	Zygomatic	Mandible
Temporal	Occipital	Maxilla	Vomer
	Sphenoid	Nasal	
	Ethmoid	Lacrimal	
		Palatine	
		Inferior concha	

EXTRA EDGE

- Skull totally consists of 22 bones.
- Mandible** is the only mobile bone in the skull; it is the strongest bone in the face.

Joints Between Cranial Bones

- Suture** (fibrous joint) is MC type of joint in skull.
- Schindelysis** (special type of fibrous joint) is between rostrum of sphenoid and ala of vomer.
- Primary cartilaginous** joint is between body of sphenoid and basilar part of occipital bone.
- Bilateral **temporomandibular** joint of **synovial** type are between mandible and temporal bone (mandibular fossa)

Anatomical Position of the Skull

- Reid's base line** is a horizontal line joining the infraorbital margin (orbital point) to the centre of the external acoustic meatus (auricular point). Conventional axial CT scan images are obtained parallel to this line.

- **Frankfurt horizontal plane** is obtained by joining the infraorbital margin to the upper margin of the external auditory meatus.

Main Skull Sutures

- **Sagittal suture**: between two parietal bones
- **Coronal suture**: between frontal bone in front and parietal bones behind
- **Lambdoid suture**: between right and left parietal bones and occipital bone behind.

Various Important "Points"

- **Vertex**: highest point of the skull on midline sagittal suture (posterior to bregma).
- **Bregma**: meeting point of coronal and sagittal sutures (represents *anterior fontanelle* of fetal skull).
- **Lambda**: meeting point of sagittal and lambdoid sutures (represents *posterior fontanelle* of fetal skull).
- **Mnemonic: "PLAB"**-Posterior fontanelle-Lambda; Anterior-Bregma!
- **Obelion** is the point on sagittal suture in between the parietal emissary foramina.
- **Asterion** is the meeting point of lower end of lambdoid suture, parietomastoid and occipitomastoid suture.
- **Inion** is the most prominent point on external occipital protuberance.
- **Nasion**: meeting point of internasal and frontonasal sutures.
- **Rhinion**: Point coinciding with lower end of internasal suture.
- **Glabella** is the median elevation between the superciliary arches.
- **Pterion**: junction of greater wing of sphenoid, squamous temporal, frontal and parietal bones. fracture at pterion may injure the *middle meningeal artery* and lead to *extradural hemorrhage*.

Major Foramina of the Skull and Structures Transmitted

Foramen ovale

Mandibular N. (CN V3) Accessory meningeal A. Lesser petrosal N. Emissary vein (connecting cavernous sinus with pterygoid venous plexus) (MALE)

Carotid canal

Internal carotid A.
Venous and sympathetic plexus around the artery.

Superior orbital fissure

CN III, CN IV, CN V1 (Ophthalmic) and CN VI Inferior ophthalmic V.
Lacrimal nerve, Frontal nerve

Contd...

Foramen spinosum

Middle meningeal A.
Meningeal branch of mandibular N. (*nervus spinosus*),
Posterior trunk of middle meningeal V.

Inferior orbital fissure

Maxillary N.
Zygomatic branch of maxillary N.
Orbital branches of the pterygopalatine ganglion
Infraorbital vessels.

Foramen rotundum

Maxillary Nerve (CN V2)

Optic canal

Optic nerve (CN II) Ophthalmic A. Central retinal V.

Foramen lacerum

Internal carotid A.
Meningeal branch of ascending pharyngeal artery
Lesser petrosal N. (branch of IX),
Greater petrosal N. (branch of VII)
Deep petrosal nerves (autonomic).

Foramen magnum

Through posterior part

Medulla oblongata
Spinal roots of accessory nerves
vertebral arteries
Posterior spinal arteries
Anterior spinal artery

Through anterior part

Apical ligament of dens
Membrana tectoria

Internal auditory/acoustic meatus

Facial N
Vestibulocochlear N
Nervus intermedius of Wrisberg
Labyrinthine vessels

Stylomastoid foramen

Facial N

Stylomastoid branch of the posterior auricular A.

Jugular foramen

CN IX, CN X and CN XI
Internal jugular V.

Hypoglossal canal

Hypoglossal N. (antr. condylar canal)

Petrotympenic fissure

Chorda tympani branch of the facial N.
Anterior tympanic artery
Anterior ligament of malleus

Other Foramina

- **Mastoid F**: Emissary vein, meningeal branch of occipital A.

Contd...

- **Tympanomastoid fissure**: Auricular branch of vagus N.
- **Parietal F**: Emissary vein from the superior sagittal sinus.
- **Supraorbital notch, F**: Supraorbital N. and vessels.
- **Infraorbital F**: Infraorbital N. and vessels.
- **Zygomaticofacial F**: Zygomaticofacial N. (branch of maxillary nerve)

- **Inclisive foramen**: Terminal part of greater
- **Palatine vessels**, terminal part of nasopalatine nerve from nose to palate.
- **Greater palatine F**: Greater palatine vessels, anterior palatine N.
- **Lesser palatine F**: Middle and posterior palatine nerves.

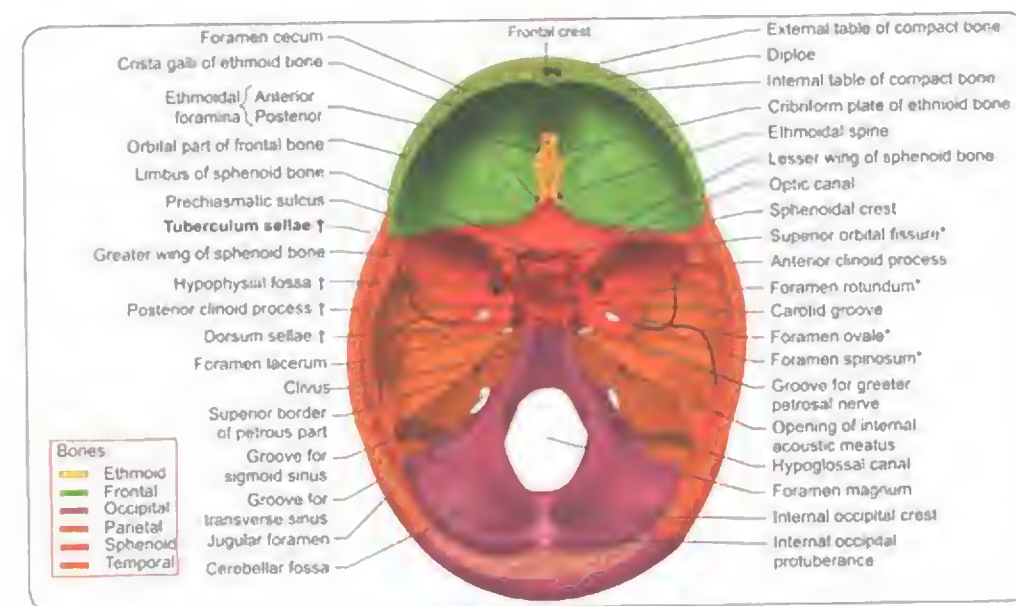


Fig. 2.70: Superior view, internal surface of cranial base

Sphenoid Bone

- Sphenoid bone is an unpaired bone that resembles the shape of a bat with outstretched wings.
- It has a body, a pair of greater wings, a pair of lesser wings and a pair of pterygoid processes.
- **Greater wing of sphenoid** presents the following foramina: foramen *Rotundum*; foramen *Ovale*; foramen *Spinosum*; canaliculus *Innominationis* and Emissary sphenoidal foramen (foramen of Vesalius) ("ROSIE").
- The *sella turcica* (*Turkish saddle*) is the hollowed out upper surface of *body of sphenoid*. It contains the *pituitary gland*.
- The *superior orbital fissure* is bounded by the body, greater wing and lesser wing of sphenoid.

Temporal bone

- Temporal bone has following parts-squamous, mastoid, petrous, tympanic and styloid process.
- **Petrous** part is the **hardest** part of temporal bone.

- At **birth**, mastoid process, mastoid air cells and styloid process are **absent**.
- **Styloid process** provides attachment to **two ligaments** (stylomandibular and stylohyoid) and **3 muscles** (stylohyoid supplied by facial nerve; stylopharyngeus by glossopharyngeal nerve and styloglossus by hypoglossal nerve).

More High Yield About Skull

- Each **maxilla** articulates with nine bones: 2 cranial (frontal and ethmoid) and 7 facial (nasal, zygomatic, lacrimal, inferior nasal concha, palatine, vomer, and the adjacent fused maxilla); It does **NOT** articulate with sphenoid.
- **Sphenopalatine foramen** opens into the *medial wall* of *pterygopalatine fossa*.
- **Optic canal** (foramen) is enclosed by lesser wing and body of sphenoid.
- **Arcuate eminence** in petrous part of temporal bone is caused by *superior semicircular canal*.

- Cartilaginous part of auditory (Eustachian) tube lies *inferior to sphenopetrosal synchondrosis*.
- **Sternberg's canal** is persistent lateral craniopharyngeal canal, lies anteromedial to foramen rotundum. Congenital intra-sphenoidal meningocele and encephalocele may arise through this canal.
- **Craniofacial angle** is 130 degrees.
- **Dorello canal** is an opening to cavernous sinus that transmits *abducent nerve*.
- **Kerckring's center of ossification** is sometimes present in posterior margin of foramen magnum at about 16th week of fetal life and fuses with occipital bone before birth.
- **Ramus of mandible** provides insertion to all the muscles of mastication.
- **Mandible** is the *second bone* to ossify in the body (both intramembranous and endochondral).
- **Angle** of the mandible is about 110 degrees in adults.
- The **highest nuchal line** of occipital bone gives attachment to galea aponeurotica and origin to occipital belly of occipitofrontalis.
- The **superior nuchal line** of occipital bone gives origin to trapezius and insertion to sternomastoid.
- **Supraorbital foramen**, **infraorbital foramen** and **mental foramen** are located in the *same vertical line* passing through them!.
- Nerves related to *spine of sphenoid* are- *auriculotemporal nerve* laterally and *chorda tympani nerve* medially.
- At birth the frontal bone has two part divided by the *metopic suture* which fuses by 8th year of life.
- Cranial vault of adult is bilamellar (has outer and inner table of compact bone and intervening vascular component called *diploe*). At birth it is unilamellar without any diploe.
- **Diploic veins** are *valveless*; have very thin endothelium supported by elastic tissue
- **Skin** of scalp has numerous *sweat glands* and *sebaceous glands* (hence *sebaceous cysts* are common in scalp).
- The fibrous strands in the *superficial fascia (connective tissue)* are fixed to blood vessels that prevents retraction of these blood vessels when injured-hence *scalp cuts bleed profusely*-can be controlled by *direct application of pressure* against the bone or by suturing.
- Aponeurotic layers consists of 2 parts-galea aponeurotica (epicranial aponeurosis) and a muscular part (frontal and occipital bellies of occipitofrontalis).

Loose subaponeurotic areolar tissue (4th layer)

- ▶ It is called **dangerous area of the scalp** since it contains emissary veins through which infection in this space may pass into the intracranial venous sinuses (intracranial venous thrombosis may occur!).
- ▶ Bleeding in this space (due to scalp injury by direct blow to skull) tends to gravitate into eyelid producing "**black eye**".
- ▶ In newborns, there is slow accumulation of blood in this space when there is intracranial hemorrhage due to fracture of skull and associated dural tear. Leakage of blood in this potentially large subaponeurotic space delays symptoms of cerebral compression-"**safety valve hematoma**".

Arterial Supply of Scalp

- The scalp is a site of free anastomosis between external and internal carotid arteries

Anteriorly	Posteriorly
Supratrochlear and supraorbital artery (branches of ophthalmic artery, a branch of internal carotid artery)	Posterior auricular artery and occipital artery (branches of external carotid artery)
Superficial temporal artery (branch of external carotid artery).	

Nerve Supply of Scalp

Anterior quadrant (in front of auricle)	Posterior quadrant (behind auricle)
Sensory: <ul style="list-style-type: none"> • Supratrochlear • Supraorbital • Zygomaticotemporal • Auriculotemporal 	Sensory: <ul style="list-style-type: none"> • Third Occipital (C2) • Lesser Occipital (C2) • Greater Occipital (C2) • Great Auricular (C2,3)
Motor: <ul style="list-style-type: none"> • Temporal branch of facial nerve (to frontal belly of occipitofrontalis) 	Motor: <ul style="list-style-type: none"> • Posterior auricular branch of facial nerve (to occipital belly of occipitofrontalis)

SCALP

Layers of the Scalp

- Skin
- Connective Tissue (superficial fascia)
- Aponeurotic layer (musculo-aponeurotic)
- Loose areolar tissue (subaponeurotic) layer
- Pericranium

More High Yield About Scalp

- During surgical incisions, the *first 3 layers* of the scalp move as one unit and can be separated from the pericranium-hence called "*scalp proper*"

FACE

FACIAL MUSCLES

- The facial muscles can broadly be split into three groups; orbital, nasal and oral.
- Orbital muscles:
 - ▶ **Orbicularis Oculi**: has inner palpebral and outer orbital part; helps in gentle and forceful eyelid closure respectively.
 - ▶ **Corrugator supercilii**: draws eyebrows together creating *vertical wrinkles on bridge of the nose*.
- Nasal muscles: **Nasalis**, **Procerus** (creates *horizontal wrinkles on bridge of nose*) and depressor septi nasi.
- Oral muscles:
 - ▶ **Orbicularis oris**: purses the lips
 - ▶ **Buccinator**: pulls cheek inwards towards teeth preventing food accumulation in that area.
 - ▶ Other small muscles acting on lips and mouth: risorius; mentalis, zygomaticus major and minor etc.
- All muscles of face/facial expression supplied by **facial nerve (CN VII)**.

Expression	Facial muscle
Grinning	Risorius
Doubt	mentalis
Blinking/Winking	Orbicularis Oculi
Frowning	Corrugator supercilii
Aggression, Concentration	Procerus
Joy	Zygomaticus major
Grief/Sadness	Depressor anguli oris

Expression

Expression	Facial muscle
Crying	Levator labii superioris
Horror and Terror	Platysma

EXTRA EDGE

- **Buccinator** muscle is *pierced by*:
 - Parotid duct
 - Buccal branch of facial nerve
 - Molar mucus glands of buccopharyngeal fascia.

FACIAL ARTERY

- Face is supplied by **facial artery**-a branch of **external carotid artery**.
- At the antero-inferior angle of the masseter muscle, the facial artery can be palpated and is called **anesthetist's artery** (since it is palpated by anesthetists here!).
- **Note: Transverse facial artery** is a branch of superficial temporal artery and NOT a branch of facial artery.

Branches of facial artery

From cervical part	From facial part
Ascending palatine	Inferior labial
Tonsillar	Superior labial
Submental Glandular (to lymph nodes and submandibular gland)	Lateral nasal and posterior (unnamed branches)

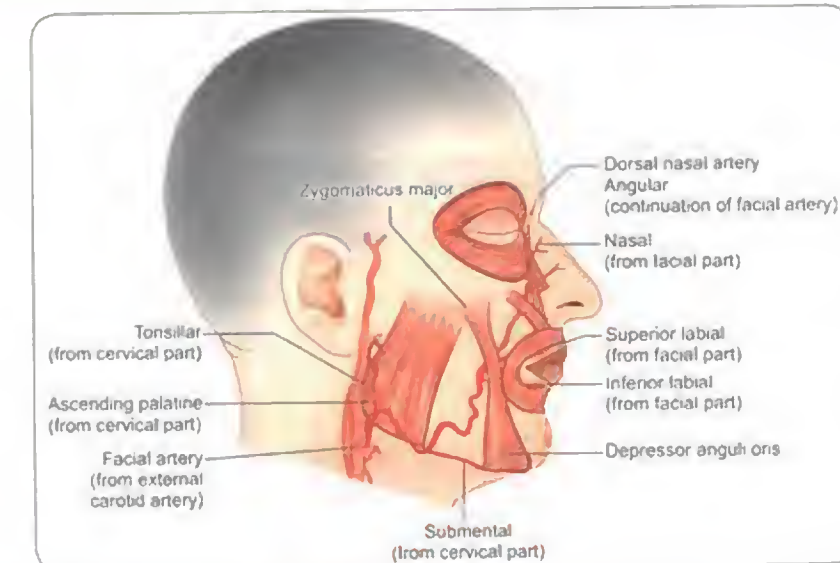


Fig. 2.71: Origin, course, branches and termination of facial artery

FACIAL VEIN

- **Facial vein** is the **largest vein of the face**; it has **NO valves**.
- **Supraorbital and Supratrochlear veins** unite to form > the **angular vein** > continues downwards as the **facial vein** > joined by the anterior division of retromandibular vein > forms the **common facial vein** > drains into **IJV**.
- Facial vein communicates through cavernous sinus by a communication between **supraorbital and superior ophthalmic** veins. Thus any infection in the upper lip

and lower part of nose may spread to cavernous sinus- hence called "**dangerous area** of the face".

SENSORY NERVE SUPPLY OF FACE

- Skin over **angle of the mandible** is supplied by **greater auricular nerve (C 2,3)**.
- Skin over **tip of nose** is supplied by **trigeminal nerve** (through **ophthalmic nerve-nasociliary** branch- continues as **anterior ethmoidal** nerve-gives of **external nasal nerve** to the **tip of the nose**).
- Sensory supply of the auricle/pinna is also an important MCQ topic and given under ENT chapter (Pg 605).

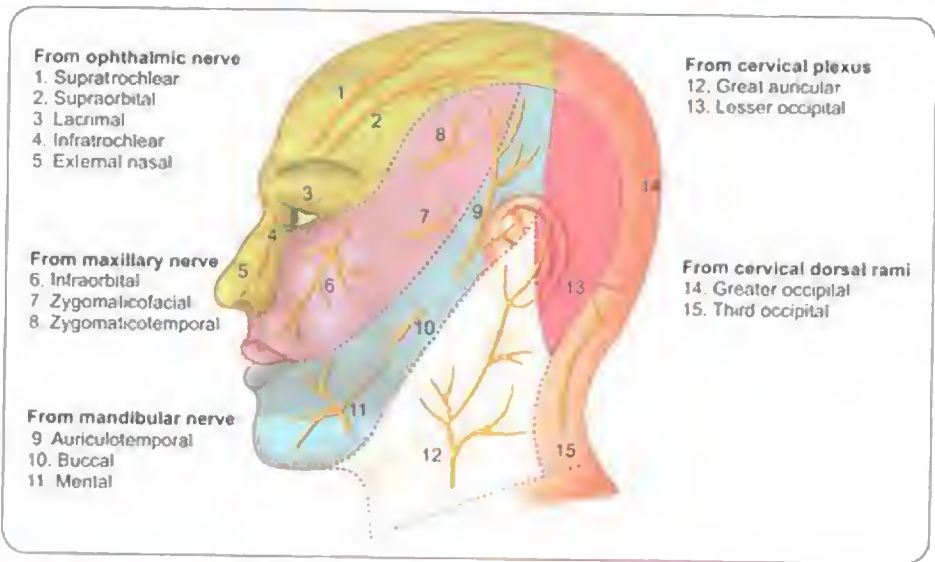


Fig. 2.72: Sensory nerves of face, scalp and auricle

MUSCLES OF MASTICATION

- All muscles of mastication mentioned below are **bilateral** structures; they are derived from **first**

branchial arch and therefore innervated by **anterior division of mandibular nerve (CN V3)**; except **medial pterygoid** by branch from **main trunk** of mandibular nerve.

Muscle	Origin and Insertion	Action	Comments
Masseter	O: Superficial part from maxillary process of zygomatic bone and deep part from zygomatic of temporal bone I: Lateral surface of ramus and angle of mandible	Elevates the mandible Protracts the mandible	Effector of the jaw jerk reflex It is hypertrophied in bruxism
Temporalis	O: Floor of temporal fossa and temporal fascia I: Coronoid process of mandible	Elevates the mandible Retracts the mandible	Fan shaped muscle; covered by temporalis fascia which can be harvested and used for myringoplasty
Lateral pterygoid	O: Upper head: Infratemporal surface and crest of greater wing of sphenoid Lower head: Lateral surface of lateral pterygoid plate of sphenoid I: Pterygoid fovea on the neck of mandible, articular disc and capsule of T-M joint	Depresses the mandible (opens the mouth). Protraction and side to side movement of mandible	Most important muscle for opening the mouth along with suprahyoid muscles

Contd...

Contd

Muscle	Origin and Insertion	Action	Comments
Medial pterygoid	O: Superficial head: Tuberosity of maxilla ; Deep Head: Medial surface of lateral pterygoid plate of sphenoid and pyramidal process of palatine bone I: Medial surface of ramus and angle of mandible	Elevates the mandible Protraction and side to side movement of jaw	Nerve to medial pterygoid supplies tensor palati and tensor tympani through otic ganglion

TEMPOROMANDIBULAR JOINT

- T-M joint is a synovial, bicondylar joint.
- It is a **complex joint** as its cavity is divided into upper and lower parts by **fibrocartilaginous articular disc**.
- Ligaments at T-M joint are:
 - Articular disc
 - Lateral T-M ligament
 - Accessory ligaments (spheno-mandibular and stylomandibular ligaments).
- Arterial supply: branches of superficial temporal and maxillary artery.
- Veins drain into pterygoid venous plexus
- Nerve supply: mandibular nerve (masseteric and auriculotemporal nerves).

Actions at T-M joint

- **Elevation** of mandible (**closing** the mouth): Masseter; Temporalis, Medial pterygoid (of both sides)
- **Depression** of mandible (**opening** the mouth): lateral pterygoid (mainly) of both sides, helped by gravity. The suprahyoid muscles help in extra-wide opening of mouth (digastric, geniohyoid, mylohyoid).
- **Protraction** (protrusion) of mandible: Lateral and medial pterygoid, Masseter.
- **Retraction** of mandible: Temporalis.
- **Side-to-side** (chewing or grinding) movements: The lateral and medial pterygoids of two sides act alternately. Masseter and temporalis assist in these movements.

EXTRA EDGE

- **Mnemonic:** Lateral pterygoid **L**owers the mandible-thus opens the mouth
- Dislocation of T-M joint occurs due to **sudden contraction of lateral pterygoids**. Patient is unable to close the mouth. To **reduce** dislocation, the surgeon puts his thumbs into the mouth and exerts downward pressure over the **lower molar teeth**, simultaneously pushing the mandible backwards.

TONGUE

Tongue-Taste Buds

- **Vallate papilla:** large in size, 8-12 in number, located immediately in **front of sulcus terminalis**

- **Fungiform papillae:** numerous **near the tip and margins** of tongue
- **Filiform/conical papillae:** cover the presulcal area of the dorsum of tongue and give a characteristic velvety appearance. They are **smallest and most numerous** of the lingual papillae.

Taste

Bitter tasted on	Back of the tongue
Sour tasted on	Along the edges
Sweet tasted on	At the tip
Salt tasted on	On the dorsum anteriorly

Muscles of Tongue

Intrinsic muscles	Are arranged in longitudinal, vertical and transverse groups. Supplied by Hypoglossal N.
Extrinsic muscles	Are Genioglossus, Hyoglossus, Styloglossus. All supplied by Hypoglossal N. and Palatoglossus by Cranial part of accessory N.

Blood Supply

- **Lingual A.**, a branch of external carotid A.

Lymphatic Drainage

Tip of tongue	→ Submental nodes
Anterior 2/3	→ Submandibular nodes
Posterior 1/3	→ Jugulo-omohyoid nodes (lymph nodes of tongue)

EXTRA EDGE

- Sour and bitter are also tasted on the palate.
- **All 4** taste modalities can be sensed on the **pharynx and epiglottis**.
- "All **GLOSSus**" muscles are supplied by hypo**GLOSSal** nerve except palatoglossus by cranial part of accessory nerve"
- **Genioglossus** is called "**safety muscle of the tongue**" since its attachment to the mandible prevents the tongue from falling backward and obstructing respiration.

PALATE

- **Hard palate** (bony) forms the anterior 4/5 of the palate. It is formed by the **maxillary** and **palatine bone**.
- **Soft palate** forms the posterior 1/5 of palate. Uvula hangs from posterior border of soft palate in the midline.
- Muscles of palate are:

- **Tensor palati** —supplied by **Mandibular N.** (first branchial arch).
- Levator palati, Palatoglossus, Palatopharyngeus, Uvula — supplied by **vagus N.**
- Cranial part of accessory N through pharyngeal branch of (Vagus Nerve).

NECK**TRIANGLES OF THE NECK**

Anterolateral aspect (side) of the neck is divided by the sternocleidomastoid muscle into anterior triangle in front of the muscle and posterior triangle behind the muscle.

Posterior Triangle

- **Boundaries:**
 - **Anteriorly**, by posterior border of sternocleidomastoid
 - **Posteriorly**, by anterior border of Trapezius
 - **Base**, by the middle third of clavicle.
- **Floor** is formed by prevertebral layer of deep cervical fascia covering the following muscles: splenius capitis, scalenus medius and levator scapulae.
- **Inferior belly of omohyoid** divides the posterior triangle into:
 - Upper larger occipital triangle and
 - Lower smaller supraclavicular (subclavian) triangle

Contents of posterior triangle

- Four cutaneous branches of cervical plexus:
 - Lesser occipital (C2)
 - Great auricular (C2,3)
 - Anterior cutaneous nerve of neck (C2,3)
 - Supraclavicular nerves (C3,4)
- Spinal accessory nerve (CN XI) —plastered to roof of posterior triangle
- Muscular branches for levator scapulae and trapezius
- Brachial plexus branches:
 - Nerve to rhomboids
 - Nerve to serratus anterior
 - Nerve to subclavius
 - Suprascapular nerve
- **Arteries:**
 - Subclavian artery
 - Transverse cervical artery
 - Occipital artery

Anterior Triangle

- **Boundaries:**
 - **Posteriorly**, by anterior border of sternomastoid

- **Medially**, by midline of front of neck
- The upper boundary (base of triangle) is formed by base of the mandible.
- The anterior triangle is further subdivided into 4 parts by the **superior belly of omohyoid** and **diagtric** muscles: (1) submental triangle (2) Digastric triangle (3) Carotid triangle (4) Muscular triangle.

1. Submental Triangle

- This is a **median (unpaired) triangle**.
- **Boundaries**
 - **Apex** is formed by the symphysis menti of the mandible.
 - On either side there is anterior belly of **diagtric** muscle.
 - Floor is formed by mylohyoid muscle
- **Contents:**
 - **Submental lymph nodes**,
 - Submental vessels and
 - Beginning of IJV.
- **Submental lymph nodes drain:** central part of lower lip, anterior part of floor of mouth, tip of tongue.

2. Digastric Triangle

- **Boundaries**
 - **Above**, by the base of the mandible.
 - **Below** by anterior and posterior belly of digastric
 - **Floor** is formed by mylohyoid, hyoglossus and middle constrictor of pharynx.
- **Contents:** All these structures are superficial to mylohyoid.
 - **Submandibular gland**,
 - Facial artery and facial vein,
 - Mylohyoid nerve and vessels,
 - Hypoglossal nerve.

3. Carotid Triangle

- **Boundaries**

- **Posteriorly** by anterior margin of sternocleidomastoid muscle
- **Superiorly** by posterior belly of digastric muscle
- **Antero-inferiorly** by superior belly of omohyoid muscle
- Floor: thyrohyoid muscle, hyoglossus muscle, middle and inferior constrictors of the pharynx.
- **Contents:**
 - **Arteries:** **Common carotid artery** with carotid sinus and carotid body; ICA; ECA (and its branches—superior thyroid A, lingual A, Facial A, Ascending pharyngeal A; occipital A).
 - **Veins:** **IJV**; Common facial vein; pharyngeal vein and lingual vein.
 - **Nerves:** **Vagus** and its superior laryngeal branch dividing into external and internal laryngeal nerves; spinal accessory nerve; hypoglossal nerve and upper root of ansa cervicalis; sympathetic trunk.

4. Muscular Triangle

- **Boundaries**
 - **Postero-inferiorly** by sternocleidomastoid muscle
 - **Postero-superiorly** by superior belly of omohyoid muscle
 - **Anteriorly** (or medially) by anterior middle line of the neck.
- **Contents:** **Infrahyoid** muscles; deep to these muscles it contains the thyroid gland, larynx and trachea.

Suboccipital Triangle

- **Boundaries:**
 - **Medially and above**, rectus capitis posterior major and minor muscles
 - **Laterally and above**, obliquus capitis superior
 - **Inferiorly**, obliquus capitis inferior
- **Roof:** by **semispinalis capitis** muscle
- **Floor:** **posterior arch of the atlas** and **atlanto-occipital membrane**.

MUSCLES OF THE NECK**Superficial Cervical Muscles**

Muscle	Origin and insertion	Nerve supply	Action	Comments
Platysma	O: Fascia covering upper part of pectoralis major and deltoid muscles I: Anterior fibres interlace with fellow of opposite side; middle fibres attached to lower border of body of mandible; posterior fibres attached to skin and subcutaneous tissue near angle of mouth.	Cervical branch of Facial nerve	Wrinkles skin of neck; depresses the mandible; pulls down the lower lip and angle of mouth as in expression of horror or surprise	A subcutaneous muscle ; Deep injury to neck always involves platysma

DEEP CERVICAL FASCIA**Investing Layer:**

- It is deep to platysma and surrounds the neck like a collar. It forms the roof of the posterior triangle of the neck.
- This layer **splits to enclose:** trapezius and sternocleidomastoid muscles; parotid and submandibular gland; suprasternal and supraclavicular spaces.

Pretracheal Fascia:

- It encloses and **suspends the thyroid gland** and forms its **false capsule**.
- On either side of thyroid gland it forms the **suspensory ligament of Berry** which fixes thyroid gland to cricoid cartilage.

Prevertebral fascia:

- Lies behind the esophagus and pharynx and in front of the prevertebral muscles.
- It forms the floor of the posterior triangle of neck.
- **Axillary sheath** is an extension of this fascia around the subclavian artery and brachial plexus. This sheath extends into the axilla.

Carotid Sheath

- A tubular sheath of fascia surrounding the **common and internal carotid arteries, IJV and vagus nerve**.
- **Ansa cervicalis** is embedded in the wall of the carotid sheath.

EXTRA EDGE

- **"Danger space"** is a potential space bounded anteriorly by the **alar fascia** and posteriorly by the **prevertebral fascia**. It extends from clivus of skull above to the posterior mediastinum at level of diaphragm. In healthy people it is indistinguishable from the **retropharyngeal space** and is a potential path for spread of infections from the pharynx to the mediastinum.

Muscle	Origin and Insertion	Nerve supply	Action	Comments
Sternocleidomastoid	O: Sternal head from anterior surface of manubrium sterni Clavicular head from upper surface of medial third of clavicle I: Outer surface of mastoid process and lateral half of superior nuchal line	Spinal accessory nerve (CN XI) is motor. Ventral rami of C2, C3 is sensory. Within the muscle, the two nerves form a communicating loop (ansa Maubrac)	When muscle of one side contracts, the head is tilted to same side simultaneously rotating the head so as to turn the face to the opposite side ; this movement occurs in an upwards sideways glance. When the muscles of both sides contract, the head and neck are flexed .	Blood supply: Upper 1/3 by occipital and posterior auricular artery; Middle 1/3 by superior thyroid A or External Carotid A; Lower 1/3 by suprascapular A (knowledge of this blood supply is important since this muscle is used for pedicle flap in neck reconstructive surgery and can help prevent flap necrosis!)

Infrahyoid Muscles

Muscle	Nerve supply	Action	Comments
Sternohyoid	Ansa cervicalis (C1, C2, C3)	Depresses hyoid bone	
Thyrohyoid	Fibres of C1 traveling through hypoglossal nerve	Depresses hyoid bone Can raise larynx if hyoid bone is fixed	
Sternothyroid	Ansa cervicalis (C1, C2, C3)	Pulls larynx downwards	It closely covers superficial surface of thyroid gland
Omohyoid	Ansa cervicalis (C1, C2, C3)	Depresses hyoid bone	Inferior belly of omohyoid divides the posterior triangle into upper occipital part and lower supraclavicular part

Suprahyoid Muscles

Muscle	Nerve Supply	Action	Comments
Digastric	Anterior belly: by nerve to mylohyoid branch of inferior alveolar branch of mandibular Posterior belly: by facial nerve	Depresses mandible; elevates the hyoid bone	Anterior belly develops from I arch mesoderm and posterior belly from II arch mesoderm
Stylohyoid	Facial Nerve	Elevates hyoid bone	Develops from II arch mesoderm
Mylohyoid	Nerve to mylohyoid branch of inferior alveolar branch of mandibular	Elevates the floor of the mouth during first stage of deglutition. Elevates hyoid, depresses mandible	Separates deep and superficial parts of submandibular gland. It forms muscular floor of oral cavity (oral diaphragm)
Geniohyoid	Ventral ramus of C1 via hypoglossal nerve	Elevates hyoid; depresses mandible	

Note

- Origin and Insertion of the suprahyoid and Infrahyoid muscles are less important from MCQ point of view and hence not mentioned here; kindly refer textbook of anatomy for the same.

SALIVARY GLANDS

Major Salivary Glands

- They are situated away from the oral cavity and secrete their secretions into oral cavity through their ducts.
- They are **parotid gland**, **submandibular gland** and **sublingual gland**.

Minor Salivary Glands

- These are located in **submucosa** of oral cavity and secrete their secretions into oral cavity directly.
- They are anterior **lingual glands**, **labial**, **buccal** and **palatal** glands and serous glands of **von Ebner**.

Gland	Histology	Development
Parotid	Mainly <i>serous</i> acini	Ectoderm
Submandibular	<i>Mixed</i> (serous + mucinous)	Endoderm
Sublingual	Mixed (but mainly <i>mucinous</i> acini)	

PAROTID GLAND

- **Largest** salivary gland; weighs **25 grams** and is **inverted pyramid** shaped.
- **Ectodermal** in origin.
- A **compound tubuloalveolar** type of gland with mainly serous acini.

Parotid Capsule

- Parotid gland is enclosed in a fascial capsule derived from **investing layer of deep cervical fascia**-it splits into two layers
 - A superficial thick, strong fascia called **parotid fascia**-attached to epimysium of masseter muscle.
 - A deep layer forming a thickened band between the ramus of mandible and styloid process-**stylomandibular ligament**-separates the **parotid gland** from the submandibular gland.

Processes of Parotid Gland

- **Glenoid process**: part of the base/superior surface of gland lodged *between the external acoustic meatus and the capsule of the T-M joint*; swelling and inflammation of this glenoid process (as in **mumps**) give rise to **pain during eating**.
- **Pterygoid process**: extension of deep part of gland between the medial pterygoid muscle and ramus of mandible

- **Facial process** is the part that extends on the face along the duct. A part of it becomes separate above the parotid duct as **accessory parotid gland**.

Relations of Parotid Gland

Superficial (Lateral surface)
<ul style="list-style-type: none">• Skin• Superficial fascia including posterior fibres of platysma, twigs of great auricular nerve and superficial parotid lymph nodes
Anteromedial surface
<ul style="list-style-type: none">• Posterior border of ramus of mandible (grooves the anteromedial surface)• Masseter attached to lateral surface of ramus and medial pterygoid to its medial surface.
Posteromedial surface
<ul style="list-style-type: none">• Mastoid process with its attached muscles- sternocleidomastoid and posterior belly of digastric• Styloid process and its attached muscle (stylo-glossus,- hyoid and-pharyngeus)• Styloid process separates the IJV and Internal carotid artery from parotid gland.• External carotid artery enters the gland from lower part of this surface; facial nerve enters through its upper part
Superior surface (Base)
<ul style="list-style-type: none">• External auditory meatus• T-M joint• Auriculotemporal nerve
Medial margin
<ul style="list-style-type: none">• Medial margin may project medially until it touches the lateral wall of oropharynx (hence also called 'pharyngeal margin')
Apex
<ul style="list-style-type: none">• Lies between the sternomastoid and angle of mandible; it overlaps posterior belly of digastric.

Structures Inside the Parotid Gland

- **Facial nerve** divides inside the gland into two main divisions called **temporofacial** and **cervicofacial**.
- The **retromandibular vein** is formed inside the gland by union of **superficial temporal** and **maxillary** veins.
- **External carotid artery** enters through **posteromedial surface** and divides into **terminal** branches (**superficial temporal and maxillary**).

Parotid Duct (Stensen's Duct)

- Parotid duct is **5 cm** long.
- It emerges from anterior border of parotid and crosses the lateral surface of **masseter** and can be palpated at the tense anterior margin of masseter.
- It then turns sharply medially to pierce the **buccal pad of fat, buccopharyngeal fascia, buccinator muscle** and the **buccal mucosa**.
- It opens in the vestibule of the mouth at the level of the **second upper molar tooth**.

Parasympathetic (Secretomotor) Innervation of Parotid Gland

- See under "otic ganglion-parasympathetic root" in topic titled "ganglia of head and neck" further below.

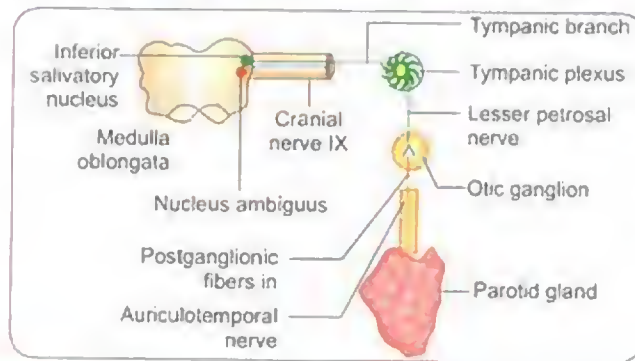


Fig. 2.73: Pathway of secretomotor nerve supply of parotid gland

SUBMANDIBULAR GLAND

- It is a **mixed** type (serous and mucinous) type of **compound racemose gland** that pours viscous secretion **against gravity** into floor of oral cavity.
- It is located in **anterior part of digastric triangle** under cover of the mandible.
- It is a **J-shaped gland** with a large superficial and small deep part continuous with each other around the **free posterior margin of mylohyoid muscle**.
- The **investing layer** of deep cervical fascia splits to enclose the submandibular gland.
- Relation to **facial artery**
 - At first facial artery grooves the posterior end of the gland.
 - Then it descends on the **lateral surface** of the gland to reach the base of the mandible at the **anteroinferior angle** of the masseter.
- **Deep part of the gland** lies in the **intermuscular interval** between the **mylohyoid** laterally and **hyoglossus** medially. It is situated between the **lingual nerve** and **submandibular ganglion** above and **hypoglossal nerve** below.

Submandibular Duct (Wharton's Duct)

- It is **5 cm** long and runs forwards on the **hyoglossus** between the **lingual and hypoglossal nerve**. At the anterior border of the hyoglossus muscle it crosses by the **lingual nerve which loops** around it.
- It opens into the **floor of the mouth**, on the summit of the sublingual papilla at the **side of the frenulum** of the tongue.

Secretomotor (Parasympathetic) Nerve Supply

- See under "submandibular ganglion-parasympathetic root" in topic titled "ganglia of head and neck" further below.
- Note that parasympathetic supply is **same for submandibular and sublingual glands**.

SUBLINGUAL GLAND

- It is the **smallest** major salivary gland; **almond** shaped; and **lies beneath the mucosa**.
- About 8-20 ducts emerge from the gland that open into the summit of sublingual fold.

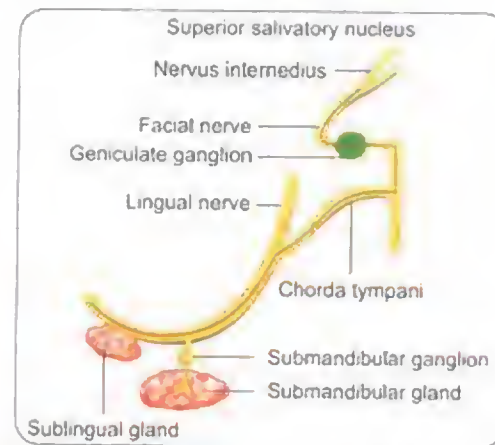


Fig. 2.74: Pathway of secretomotor nerve supply to submandibular and sublingual salivary glands

EXTRA EDGE

- **Submandibular and sublingual** glands are **endodermal** in origin. In addition, other glands of the digestive tract like the **liver and pancreas** also are **endodermal** in origin except the **parotid** gland which is **ectodermal**.
- **80% of salivary calculi** occur in **submandibular gland** since its secretions are highly viscous; 80% of submandibular stones are radio-opaque.
- Three **cranial nerves are at risk during removal of the submandibular gland**:
 1. The marginal mandibular branch of the facial nerve
 2. The lingual nerve
 3. The hypoglossal nerve.
- **Ranula** is a large mucocoele arising from **sublingual gland**.

NERVES OF THE HEAD AND NECK

CERVICAL SYMPATHETIC GANGLIA

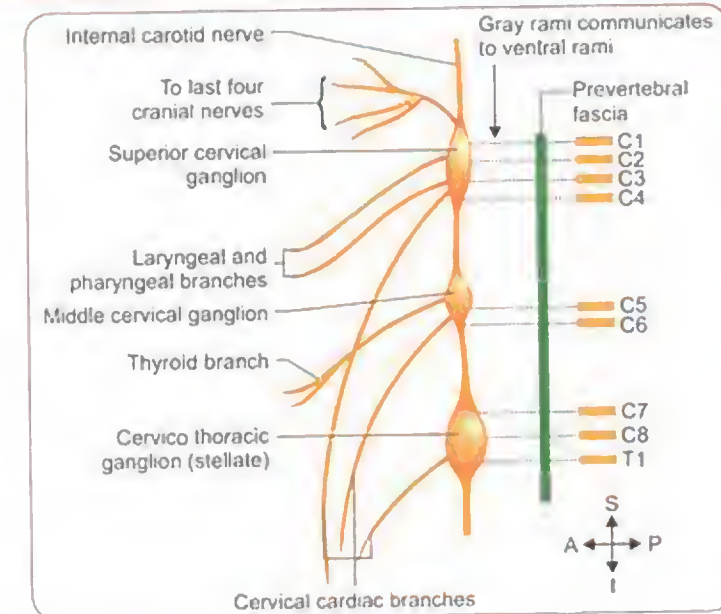


Fig. 2.75: Cervical sympathetic chain and its branches

Formation	Location	Branches
Superior Cervical Ganglion <ul style="list-style-type: none"> • Formed by fusion of C1-C4 cervical ganglia 	<ul style="list-style-type: none"> • It is the largest cervical ganglion. • Lies opposite C2, C3 vertebrae. 	<ul style="list-style-type: none"> • Grey rami communicates to C1-C4 cervical spinal nerves. • Internal carotid nerve; forms plexus around ICA • Branches to external carotid and common carotid arteries forming plexus around these arteries. • Laryngo-tracheal branches • Left and right superior cervical cardiac branch which takes part in superficial and deep cardiac plexus respectively.
Middle Cervical Ganglion <ul style="list-style-type: none"> • Formed by fusion of C5, C6 cervical ganglia 	<ul style="list-style-type: none"> • It is the smallest cervical ganglion • Lies opposite C6 vertebra • It lies on inferior thyroid artery 	<ul style="list-style-type: none"> • Grey rami communicates to C5-C6 cervical spinal nerves. • Middle cervical cardiac branch • Branches to parathyroid and thyroid • Anso subclavia winds around the subclavian artery and connects the middle and inferior cervical ganglia.
Inferior Cervical Ganglion <ul style="list-style-type: none"> • Formed by fusion of C7, C8 cervical ganglia and the T1 thoracic ganglion-hence, "cervicothoracic ganglion" It is irregular/star shaped-hence also called the "stellate ganglion" 	<ul style="list-style-type: none"> • Lies in scoleno-vertebral triangle; behind first part of vertebral artery and in front of neck of first rib. 	<ul style="list-style-type: none"> • Grey rami communicates to C7-C8 and cervical spinal nerves and T1. • Inferior cervical cardiac branches • Branches forming sympathetic plexus around subclavian and vertebral arteries. • Anso subclavia connect it to the middle cervical ganglion

EXTRA EDGE

- Stellate ganglion block causes **Horner's syndrome**-has been described in detail under 'regional blocks' in anesthesia chapter (Pg 1139).

- Out of the 6 cervical cardiac branches (superior, middle and inferior), **only left superior cervical cardiac** branch joins the **superficial cardiac plexus**; all others join the deep cardiac plexus!

GANGLIA OF HEAD AND NECK

- Most parasympathetic ganglia are **terminal/intramural ganglia** since they lie *within the organs* that they innervate. The **exceptions** are four paired parasympathetic ganglia of the head and neck mentioned in the table below.
- Each parasympathetic ganglion has:
 - Sensory root:** that contains general sensory afferent (GSA) fibres that do NOT synapse in the ganglion.

Ganglion	Parasympathetic root	Sympathetic root	Sensory root
Otic ganglion <ul style="list-style-type: none"> Topographically related to- Mandibular nerve (medial to mandibular nerve and just below foramen ovale). Functionally related to- Glossopharyngeal nerve 	Pre-ganglionic fibres begin in Inferior salivatory nucleus → glossopharyngeal nerve → tympenic branch of glossopharyngeal nerve → tympenic plexus → lesser petrosal nerve → otic ganglion (relay ganglion) → Post-ganglionic fibres pass through auriculotemporal nerve to innervate parotid gland . Thus: Lesser petrosal nerve is preganglionic and auriculotemporal nerve is post-ganglionic.	By sympathetic plexus around middle meningeal artery	By auriculo-temporal nerve
Submandibular Ganglion <ul style="list-style-type: none"> Topographically related to- Lingual branch of mandibular nerve Functionally related to- Chorda tympani branch of facial nerve 	Preganglionic fibres arise in the superior salivatory nucleus in the pons → travel in facial nerve and leave through its → chorda tympani branch → this joins the lingual nerve in Infratemporal fossa → passes to submandibular ganglion → post-ganglionic fibres enter the submandibular directly and sublingual glands through lingual nerve.	From sympathetic plexus around facial artery which contains postganglionic fibres from superior cervical ganglion	Lingual nerve
Pterygo-palatine Ganglion (spheno-palatine) <ul style="list-style-type: none"> Topographically related to- Maxillary nerve Functionally related to- Facial nerve 	Preganglionic fibres from superior salivatory nucleus in pons come through greater petrosal nerve (branch of facial nerve) which unites with deep petrosal nerve to form the nerve of pterygoid canal (Vidian nerve) . ONLY fibres of greater petrosal nerve relay in the ganglion. Post-ganglionic fibres pass through zygomatic nerve or pass through orbital branches to supply lacrimal gland . Also nasopalatine nerve supplies nasal and palatal glands	Sympathetic plexus around internal carotid artery through deep petrosal nerve	Maxillary nerve

Ganglion	Parasympathetic root	Sympathetic root	Sensory root
Ciliary Ganglion <ul style="list-style-type: none"> Topographically related to- Nasociliary nerve (branch of ophthalmic division of trigeminal nerve) Functionally related to- Oculomotor nerve 	Preganglionic fibres begin from Edinger-Westphal nucleus , join oculomotor nerve and then pass through its branch to inferior oblique to relay in the ciliary ganglion. Post-ganglionic fibres pass through short ciliary nerves to supply sphincter and dilator pupillae muscles.	From plexus around ophthalmic artery	Nasociliary nerve

EXTRA EDGE

- Nerve of the pterygoid canal (Vidian nerve)** is formed by the union of **deep petrosal** nerve and **greater petrosal** nerve in the **foramen lacerum**. Irritation of the Vidian nerve causes **lacrimation** and **excessive secretion of nasal and palatine glands** (typical features of **allergic rhinitis** or **hay fever**)—hence this nerve is called the 'nerve of hay fever' and the **pterygopalatine ganglion**, the 'hay fever ganglion'.

- Parasympathetic (secretomotor) root:** contains preganglionic parasympathetic fibres that terminate in the ganglion and the postganglionic fibres in turn project to target organs.
 - Sympathetic (vasomotor) root:** contains postganglionic fibres that do NOT synapse in the ganglion.
- Note:** Only **Otic ganglion** has a **motor root** (from nerve to medial pterygoid) in addition to the above three standard roots.

VERTEBRAL COLUMN AND SPINAL CORD

VERTEBRAE

- The vertebral column is made up of **33 vertebrae** — 7 cervical, 12 thoracic, 5 lumbar, 5 sacral (fused to form sacrum) and 4 coccygeal (fused to form coccyx).
- Length of vertebral column** in adult male = **70 cm** and in adult female = **60 cm**; vertebral bodies contribute 4/5 and IV discs contribute to 1/5 length of vertebral column.
- Each vertebra consists of
 - Body (centrum)**—weight bearing part
 - Vertebral arch:** the part that protects the spinal cord and is formed by **pedicle laterally** and **laminae posteriorly**.
 - Two **transverse processes** and one **spinous process**.
 - Four **articular facets:** two superior and two inferior.
- Intervertebral foramen** contents are: (1) spinal nerve and its recurrent meningeal branch (2) spinal branches of regional arteries (3) intervertebral veins.
- Curvatures of vertebral column
 - Primary curvature** with **forward concavity:** thoracic and sacral parts of vertebral column
 - Secondary curvatures** with **forward convexity** develop in **cervical and lumbar** region after birth.
- Intervertebral disc** is an **avascular structure** and is composed of 2 parts:
 - Inner nucleus pulposus:** a remnant of **notochord**.
 - Outer annulus fibrosus** made of **fibrocartilage:** develop from **sclerotome** of the **somite**.

Cervical Vertebrae (C1-C7)

- The number of **cervical vertebrae** is **remarkably constant** at 7 (coccygeal are most variable).
- Cervical vertebrae **3-6 are typical** while, **1,2,7 are atypical**.

Characteristic features of typical cervical vertebrae are:

- Foramen transversarium** is present **ONLY** in the **cervical vertebrae**. Foramen transversarium of C1-C6 transmit vertebral artery, vertebral vein and sympathetic plexus BUT that of **C7** transmits **ONLY** vertebral vein
- Body is small** and broad transversely.
- They possess **bifid spinous processes**, which is absent in C7.
- Vertebral foramen is **large and triangular**.
- Superior articular facet** is directed **upwards and backwards** and inferior articular facet is downwards and forwards.

- C1 vertebra = Atlas.** "Atlas in Greek mythology carries the globe on his shoulders, hence the C1 vertebra, which supports the skull is atlas".

- C2 = Axis;** an upward projection present on the C2 vertebra (axis) is called **Dens** or **odontoid process**.
- C7 = vertebra prominens** (due to most prominent spine).
- Uncovertebral joints of Luschka** are present at posterolateral margins of IV discs of C3-C6.
- Anterior tubercle on transverse process of **C6** is prominent and called **carotid tubercle** or **Chassagnac's tubercle**. It is related to **common carotid artery** which can be palpated against it.
- Erb's point** is opposite Chassagnac's tubercle. **Cricoid cartilage** is at level of C6.

Craniovertebral Joints

- These articulations take place between the **occipital condyles, atlas and axis**. They are synovial joints.
- Atlanto-Occipital joints:**
 - They are **2** in number (one on each side)—**ellipsoid** type—between C1 and occipital condyles.
 - Flexion** and **extension** occur at the **atlanto-occipital joint**. (**nodding the head** as in indicating 'yes?'); **sideways tilting of the head** also occurs at this joint
- Atlanto-Axial joints:**
 - 3** in number—one **median (pivot)** type and two **lateral (plane)** type atlanto-axial joints.
 - Side to Side rotational movement** occurs at the **atlanto-axial joint**; also turning the head side-to-side (as in indicating 'no!' or looking to the right and left while crossing the road) also occurs at this joint.
 - There is **NO** intervertebral disc between atlas and axis.

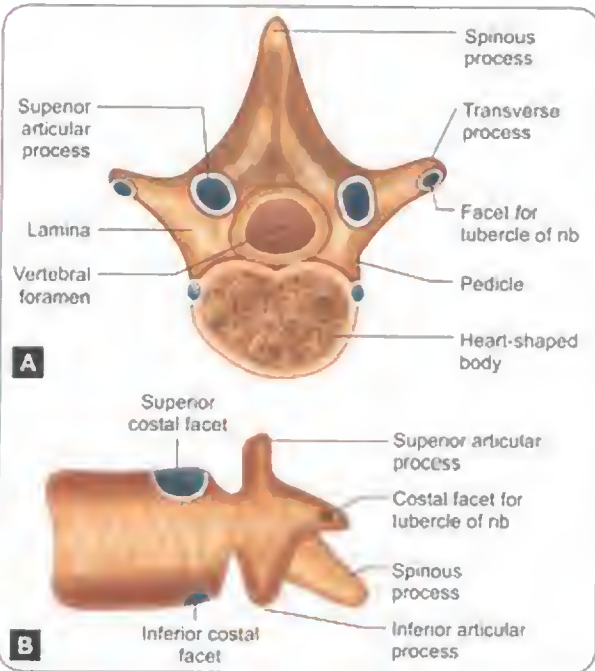
Ligaments Connecting Atlas, Axis and Occipital Bone

- Anterior atlanto-occipital membrane** connects anterior margin of foramen magnum to anterior arch of atlas—it is the continuation of **anterior longitudinal ligament**.
- Posterior atlanto-occipital membrane** connects posterior margin of foramen magnum to posterior arch of atlas. This ligament has a free inferolateral margin; **vertebral artery** enters the vertebral canal by passing deep to this edge. It represents the **ligamentum flavum** in this region of the spine.
- Apical ligament** passes upward from tip of **dens** to the anterior margin of foramen magnum. It is a **remnant of the notochord**.
- Alar ligaments** are attached to the side of the **dens** and above to medial sides of occipital condyles.
- Membrana tectoria (occipitoaxial ligament)** is the upward continuation of **posterior longitudinal ligament**.

- **Cruciate ligament** has a strong transverse part which is the **transverse ligament of the atlas**-major stabilising ligament at the atlanto-axial joint.

Thoracic Vertebrae (T1-T12)

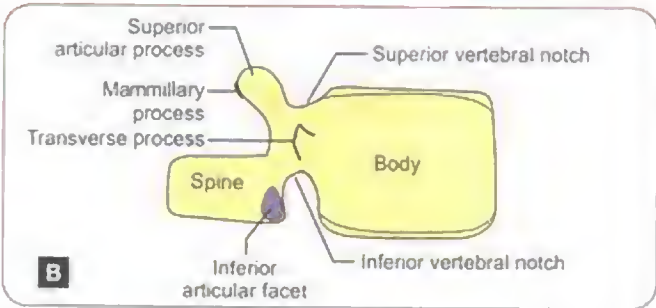
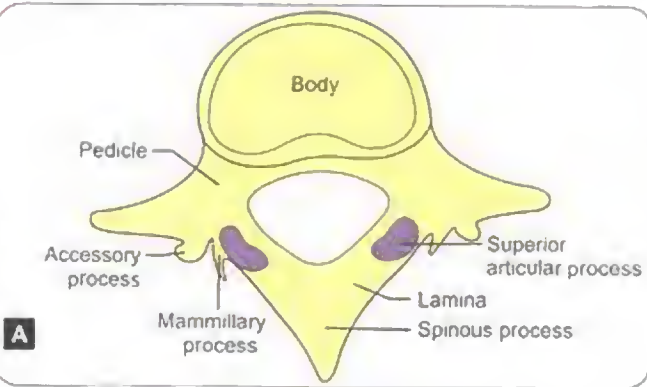
- Thoracic vertebrae are distinguished by:
 - The presence of **costal facets** for the **articulation of the heads of ribs**;
 - Body is intermediate in size between the cervical and lumbar vertebrae.



Figs. 2.76A and B: Features of typical thoracic vertebra (A) Superior view; (B) Lateral view

Lumbar Vertebrae (L1-L5)

- **Lumbar vertebra** has a large body;
- It **does not have costal facets nor transverse process foramina**.



Figs. 2.77A and B: Features of typical lumbar vertebra as seen from above and from lateral side

SPINAL CORD

- **45 cm long**, extends from the **upper border of Atlas (C1)** to the **lower border of L1**
- **Note:** In **newborns** spinal cord terminates at **L3** level. Up to the **third month** of intrauterine development, the spinal cord extends throughout the length of the vertebral canal.
- Here it narrows to a sharp tip, the **conus medullaris**. Below this the nerve roots form the **cauda equina**.
- The conus is continuous below with the **filum terminale**, a fine connective tissue filament, which descends upto the **dorsum of the first coccygeal segment**.
- Spinal cord has two enlargements-**cervical and lumbar** enlargement.
- Spinal cord **circumference** is **maximum at C6** level (38 mm).

Spinal Nerves

- The spinal segments **as a rule** always lie **above** their numerically corresponding vertebral spines.
- For **C1-C7**, nerves exit via the **Intervertebral foramina above the corresponding vertebra**; **C8** exits between seventh cervical and first thoracic vertebra; **nerves T1 and below** exit **below the corresponding vertebra**.
- Spinal cord is made up of **31 spinal nerves**—8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
- Each **spinal nerve** is a **mixed nerve** made of sensory and motor nerve fibres.
- Each spinal nerve is attached to spinal cord by dorsal and ventral roots; **ventral root is motor** and **dorsal root is sensory**. Just proximal to the junction of the two roots, the dorsal root is marked by a swelling called **dorsal root ganglion** (spinal ganglion) containing **pseudounipolar neuron**.

Meninges of Spinal Cord

- Meninges of the spinal cord are **outer dura mater**, **middle arachnoid mater** and **inner pia mater**.
- The spinal cord extends only **upto L1** but the dura and arachnoid along with **Subarachnoid Space** containing CSF extends **upto the lower border of S2 (SS = S2?)**. Between these two levels, the subarachnoid space around filum terminale is **roomy** and contains a pool of CSF called **lumbar cistern**. In this region, a needle can be introduced into subarachnoid space without injuring the spinal cord-**lumbar puncture**.
- **Lumbar puncture** is usually done at the **L4-L5** (or **L3-L4**) interspaces.

Blood Supply of Spinal Cord

- A **single median anterior spinal artery** supplies the **anterior 2/3** of the cord (**branch of the vertebral artery**) and
 - **Two posterior spinal arteries** (branches of the 4th part of vertebral) supply the remainder
 - **Radicular arteries** supply the roots of spinal nerves
 - **Arteria radicularis magna** of **Adamkiewicz** (from 10th or 11th posterior intercostal or subcostal artery) supplies **lower 2/3 of spinal cord**.
- **Modifications of Pia Mater:**
 - **Filum terminale** as described above
 - **Linea splendens** is a thickened band of pia mater along the anterior median fissure of the spinal cord.
 - **Ligamenta denticulata:** are lateral extensions of pia mater between the attachments of dorsal and ventral nerve roots.

VERTEBRAL LEVELS

Vertebral level	Structures
C1	Dens Spinal root of CN XI crosses transverse process of atlas Superior cervical ganglion
C2	Superior servical ganglion
C3	Body of hyoid bone
C4	Bifurcation of common carotid artery Upper border of thyroid cartilage
C6	Cricoid cartilage; Vertebral artery enters foramen transversum; middle cervical ganglion; Carotid tubercle of Chassaignac; Inferior thyroid artery cross to thyroid Spinal cord circumference is maximum (38 mm)

Contd...

Contd...

Vertebral level	Structures
C7	First easily palpable spinous process; Stellate ganglion
C3-C6	Extent of Larynx
T2	Superior border of scapula
T3	Medial end of spine of scapula Spine of T3 is posterior end of oblique fissure of lung; end of pre-vertebral fascia
T4	End of arch of aorta; azygous vein enters SVC
T4/T5	Manubriosternal junction (Angle of Louis); Start and end of arch of aorta; bifurcation of trachea at carina
T5	Thoracic duct crosses midline from right to left
T7	Inferior angle of scapula
T8	Inferior vena Caval opening in diaphragm; Left phrenic N pierces diaphragm; Hemi-azygous vein crosses to left
T9	Xiphisternal joint
T10	Oesophageal opening in diaphragm
T12	Aortic opening in diaphragm; Cellac axis; splanchnic nerves pierce crura; sympathetic trunk passes into abdomen Thoracic duct begins as a continuation of the upper end of cisterna chyli
L1	End of spinal cord (conius medullaris) Transpyloric plane Superior mesenteric artery comes off aorta
L1/L2	Azygos vein forms from right subcostal and ascending lumbar veins
L3	Right crus of diaphragm Inserts into body of L1 + L2 + L3 Inferior mesenteric artery comes off aorta
L4	Abdominal aorta bifurcates Iliac crest and supracristal plane Isthmus of horseshoe kidney
L4/L5	Site for lumbar puncture
L5	IVC formed from common iliac veins Tubercle of Iliac Crest
L5/S1	Bifurcation of common iliac arteries
S2	End of dural sac of spinal cord Axis of sacrum; mid point of sacro-iliac joint Lower attachment of small bowel mesentery Posterior superior iliac spine
S3	Start of rectum

EXTRA EDGE

- Bifurcations occur at 4th vertebral levels-i.e.,
 - C4-Common carotid bifurcates
 - T4-Trachea bifurcates
 - L4-abdominal aorta bifurcates

BRAIN

CRANIAL MENINGES

- The **outer dura**, **middle arachnoid** and **inner pia** mater are called cranial meninges.
- Dura mater = **pachymeninx**; arachnoid + pia mater = **leptomeninges**.

Dura Mater

- **Thickest** and **toughest** membrane covering the brain
- Dura mater has an **outer (endosteal) layer** and **inner (meningeal layer)**
- The dura mater forms **folds** by reduplication of its **meningeal layer**; these dural folds help in **stabilising the brain** during movements of the head. The four dural folds are:
 - **Falx cerebri**: "sickle" shaped fold of dura mater that separates the two **cerebral hemispheres**.
 - **Superior sagittal sinus** is inside its attached superior margin
 - **Inferior sagittal sinus** is inside its free inferior margin.
 - **Straight sinus** is along its line of attachment to tentorium cerebelli.
 - **Falx cerebelli**: Separates the **two lobes of cerebellum** and contains the **occipital sinus**.
 - **Tentorium cerebelli**:
 - **Tent shaped** fold of dura mater that forms roof of posterior cranial fossa.
 - It separates **occipital lobes above from the cerebellar lobes below**;
 - It takes the **weight of cerebrum off the cerebellum**!
 - Venous sinuses related to tentorium cerebelli are: **superior petrosal sinus**, **transverse sinus** and **straight sinus**.
 - Cavum trigeminale (**trigeminal cave** or **Meckel's cave**) is formed by evagination of meningeal layer of tentorium cerebelli over trigeminal impression on the **petrous temporal bone**-it lodges the **trigeminal ganglion**.
 - **Diaphragma sellae**:
 - It is a **circular** dural fold that forms **roof of the hypophyseal fossa** (sella turcica) which lodges the pituitary gland
 - It contains the **anterior and posterior intercavernous sinuses**.

Craniovertebral Joints

Dura mater is supplied by **mainly by** branches of the **trigeminal nerve (CN V)** as described below:

Craniovertebral Joints

- In anterior cranial fossa: from **anterior and posterior ethmoidal nerves** (branches of ophthalmic division of CV V) and meningeal branches of **maxillary** and **mandibular** nerves.
- In middle cranial fossa: from **nervus spinosus** (branch of mandibular nerve); meningeal branches of maxillary nerve and directly from **trigeminal ganglion**.
- In posterior cranial fossa: from meningeal branches of **upper cervical nerves**; **tentorial nerve** (recurrent meningeal branch of ophthalmic nerve); meningeal branch of **vagus (CN X)** and **hypoglossal (CN XI)** nerves.

Arachnoid Mater

- Middle arachnoid mater is very thin and it projects as **villi and granulation** in the venous sinuses (especially **superior sagittal sinus**).
- The arachnoid granulations or **Pacchionian bodies** are **hypertrophied arachnoid villi**.

Spaces Related to Meninges

- **Extradural (Epidural) space**: a potential space between the endosteal dura and inner surface of cranial bones. It contains **middle meningeal** vessels and rupture can cause **extradural hematoma**.
- **Subdural** space: potential space between the outer dura mater and middle arachnoid mater; it is traversed by **superior cerebral veins** which drain into superior sagittal sinus; rupture of these veins can cause **subdural hematoma**.
- **Subarachnoid** space: between the arachnoid and pia mater. It contains **CSF** and the larger arteries and veins of the brain.

Subarachnoid Cisterns

There are certain places where the subarachnoid space is wide and filled with larger pool of CSF-hence called cisterns.

Cistern	Location	Contents
Cerebromedullary cistern-largest-hence 'cisterna magna'	Between inferior surface of cerebellum and posterior aspect of medulla	Receives CSF from IV ventricle through foramen of Magendie and communicates with spinal subarachnoid space; this cistern is used for cisternal puncture through sub-occipital triangle

Contd...

Contd

Cistern	Location	Contents
Cisterna Pantis	Anterior to upper part of pons and medulla	Vertebral and Basilar artery
Interpeduncular cistern (cisterna basalis)	Overlies Interpeduncular fossa at base of brain	Contains circle of Willis
Cisterna ambiens (A.k.a Cistern of great cerebral vein, Monro's canal)	On posterior aspect of midbrain inferior to splenium of corpus callosum	Great cerebral vein of galen; Pineal body protrudes into it
Cistern of lateral fossa	Within lateral sulcus	Middle cerebral vessels

CEREBRUM

- Cerebrum is **largest part** of brain; it is made up of two cerebral hemispheres separated by the **median longitudinal fissure**.
- The two hemispheres are **connected by corpus callosum**.
- **Lateral ventricle** is the cavity of each cerebral hemisphere.
- **Grey matter**: Consist of **cell bodies of neurons and axons and dendrites** which are mostly **unmyelinated**.

Functional Areas of Cerebral Cortex (Brodmann Areas)

Area	Name and location	Function
3,1,2	Primary sensory cortex Lies in the postcentral gyrus in posterior part of paracentral lobule	The contralateral body is represented upside down in the sensory cortex (sensory homunculus). Concerned with general sensation and proprioceptive perception in opposite half of the body
5,7	Sensory association areas Lies in superior parietal lobule	Helps the person in recognising object placed in the hand without seeing it (stereognosis).
4	Primary voluntary motor cortex Occupies entire precentral gyrus and anterior part of paracentral lobule.	This area controls voluntary movements of the opposite half of the body. The human body is represented upside down in the motor area (motor homunculus); the more skilled the movements, the larger is the representation in the motor cortex- thus hand has large representation with thumb having largest representation . Similarly lips, jaw and tongue have large area (muscles of vocalisation) > muscles of mastication > salivation.
6	Premotor area Located anterior to motor area (in front of precentral gyrus) and occupies the posterior parts of superior, middle and inferior frontal gyri.	This area is responsible for performance of skillful acts , which are learned through repetitive efforts.
8	Frontal eye field Lies in middle frontal gyrus anterior to precentral gyrus	Stimulation of this area causes both eyes to move to the opposite side- conjugate movements

Contd...

- **White matter**: Consists predominantly of **Myelinated fibres** ("W= ultra M!")
- There are **4 lobes**-frontal, temporal, parietal and occipital lobes which are demarcated with the help of lateral, central and parieto-occipital sulci.

Cerebral Sulci

- **Sulci and Gyri**: Surface of the brain is folded into **sulci** (depressions) and **gyri** (raised areas).
- Four main types of sulci on cerebrum are:
 - **Limiting sulcus**: separates areas of cortex which differ in structure and function-ex-**central sulcus**.
 - **Axial sulcus**: develops along the long axis of a rapidly growing cortical area; ex: **posterior part of calcarine sulcus**.
 - **Complete sulcus**: is one which reaches the wall of the ventricle to produce an elevation there; ex: **calcarine sulcus** and **collateral sulcus**.
 - **Secondary sulcus**: depends on external factors for its formation; ex: **lateral sulcus** and **parieto-occipital sulcus**.
- **Central sulcus (fissure of Rolando)** Runs obliquely downwards from the superior margin of the brain almost to the lateral fissure.
- **Lateral sulcus (Sylvian fissure)**: Separates the **temporal lobes inferiorly from frontoparietal lobes superiorly**.

Contd...

Area	Name and location	Function
9,10,11,12	Prefrontal cortex Anterior part of frontal lobe (area 12 on orbital surface of frontal lobe)	This area is regarded as "association cortex"; it has numerous connections with cortex of other three lobes. Also connected to dorsomedial thalamic nucleus (lesions causes personality change)
17	Primary visual cortex It lies in the calcarine fissure of the occipital pole ; A.k.a striate cortex since the striae of Gennari (typical white stripe of geniculocalcarine fibers) is visible with naked eye. This area receives the optic radiation, which brings impulses from the temporal half of ipsilateral and nasal half of contralateral retina. Thus, left half of visual field is represented in the right visual cortex and vice versa. The macula is represented on the occipital pole (tip)	This area is concerned with perception of color, size, form and motion
18,19	Visual association area (<i>parastriate and prestriate cortex</i>)	Responsible for interpretation of visual impulse reaching area 17
22	Wernicke's speech area (sensory speech area) lies in the posterior part of the superior temporal gyrus . Also includes part of area 39 (<i>angular gyrus</i>) and area 40 (<i>supramarginal gyrus</i>)-both on inferior parietal lobule .	Area 22 is responsible for comprehension of received speech. Area 39 is responsible for visual speech or reading; area 40 is responsible for recognition of and naming of objects by touch and proprioception.
41	Primary auditory (acoustic) area ; It occupies the anterior transverse temporal gyrus (Heschl's gyrus) on the superior aspect of superior temporal gyrus (in the depths of the lateral fissure-hence hidden from view)	This area receives auditory radiations from the medial geniculate bodies conveying impulses from organ of Corti of both sides via multisynaptic auditory paths of both sides.
22	Auditory association area located on posterolateral part of superior temporal gyrus; part of this area is included in Wernicke's speech area.	This area is necessary for interpretation of sound impulses in light of past experiences.
28	Entorhinal area (olfactory area) located in the uncus, which is the anteromedial part of parahippocampal gyrus.	
44, 45	Broca's speech area (motor speech area) Lies in the posterior part of the inferior frontal gyrus	Responsible for spoken speech (rhythm of speech)
49	Gustatory area located in parietal operculum (posteroinferior part of postcentral gyrus)	

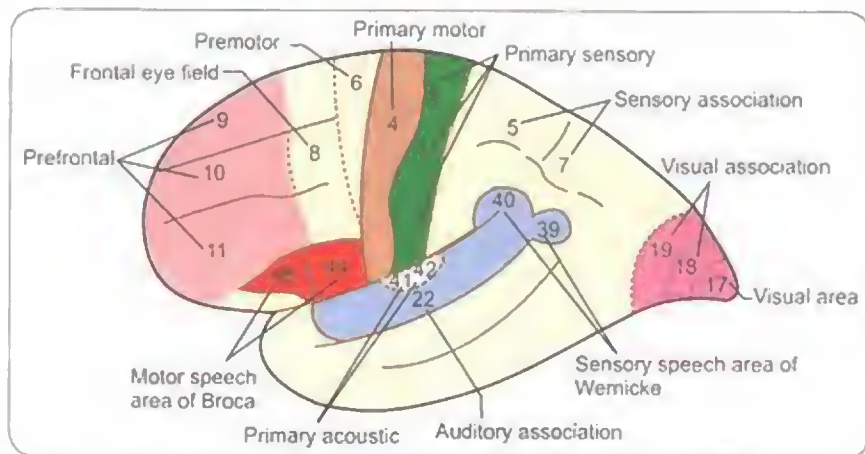


Fig. 2.78: Functional areas of Brodmann on superolateral surface of left cerebral hemisphere

WHITE MATTER OF CEREBRUM

The interior of each cerebral hemisphere consists of a core of white matter (myelinated nerve fibres) which is classified into 3 types:

1. **Association fibres**: connect one functional area in one cerebral hemisphere to another functional area in the same hemisphere.
2. **Comissural fibres**: cross the midline and connect identical parts of the two hemispheres.
3. **Projection fibres**: connect the cerebral cortex to other regions of the brain and spinal cord by ascending and descending fibres.

Association fibres

- Cingulum
- Superior longitudinal fasciculus
- Inferior longitudinal fasciculus
- Uncinate fasciculus

Projection fibres

- Corona radiata
- Internal capsule
- Fornix

Commissural fibres

- Anterior commissure (**cupid's bow** shaped)
- Posterior commissure
- Habenular commissure
- Hippocampal commissure
- Corpus callosum (**largest commissure** of the brain)

Corpus Callosum

- Corpus callosum is made up of a large mass of nerve fibres that connect the **homotopic** (symmetrical) and

heterotopic (anatomically different but functionally similar) areas of two cerebral hemispheres. It helps in coordinating activity between the two hemispheres.

- The **indusium griseum** is a **thin layer of grey matter** which covers the superior surface of the corpus callosum.
- It is the **largest commissure** of brain and located in the **floor of the median longitudinal fissure**.
- Parts and connections of corpus callosum are given in below table

Genu (thick anterior end)	Fork-like bundle of fibres (foreceps minor) interconnect the two frontal lobes
Rostrum (prolongation of genu to upper end of lamina terminalis)	Fibres interconnect orbital surface of frontal lobes
Trunk/body	Fibres project bilaterally to wide areas of cerebral cortex and are intersected by fibres of corona radiata
Splenium (posterior bulbous end)	Fork-like bundle of fibres (foreceps minor) interconnect the occipital lobes

Internal Capsule

- There are a large number of nerve fibres interconnecting the cerebral cortex with centres in the brainstem and spinal cord, and the thalamus.
- Most of these fibres pass through the interval between the **thalamus and caudate nucleus medially** and the **lentiform nucleus laterally**. This region is called the **internal capsule**.

Part	Descending fibres	Ascending fibres	Arterial supply
Anterior limb	Corticopontine fibres	Anterior thalamic radiation	lateral striate branches of middle cerebral artery (Charcat's artery) Recurrent branch of anterior cerebral artery (Huebner's artery)
Genu	Corticonuclear fibres Corticospinal fibres for head and neck	Superior thalamic radiation	Internal carotid artery (direct branches) Recurrent branch of anterior cerebral artery
Posterior limb	Corticospinal fibres for limb and trunk Corticorubral fibres radiation	Superior thalamic radiation	Anterior choroidal artery (branch of ICA) Lenticulostriate branches of middle cerebral artery
Retrolentiform	Corticopontine fibres	Optic radiation	Anterior choroidal artery Deep optic artery (branch of MCA) Posterior cerebral artery (central branches)
Sublentiform	Corticopontine fibres	Auditory radiation	Anterior choroidal artery Posterior cerebral artery (central branches)

Diencephalon

Pars dorsalis

- Thalamus (dorsal thalamus)**
 - Described separately below
- Metathalamus**
 - Medial and lateral geniculate
- Epithalamus**
 - Described separately below

Pars ventralis

- Subthalamus (ventral thalamus)**
 - Subthalamic nucleus
 - Reticular nucleus
 - Zona incerta
 - Perigeniculate nucleus
 - Fields of Forel (see below)

Hypothalamus

Thalamus

- Major synaptic relay station** and is concerned with processing of ascending sensory information to the cerebral cortex (except olfactory pathway).
- Every thalamic nucleus **except reticular nucleus** sends axons to different parts of cortex; the output of reticular nuclei is mainly to other thalamic nuclei.
 - Ventral posterior nucleus, lateral part (VPL): Body sensation (proprioception, pressure, pain and touch, vibration via dorsal columns, spinothalamic tract)
 - Ventral Posterior nucleus, Medial part (VPM): Facial sensation (via CN V) "Very Poor Makeup ruins your Face!"
 - Ventral anterior/lateral nuclei: Motor.
- Blood supply** of thalamus: **Posterior communicating, posterior cerebral and anterior choroidal arteries**

Metathalamus

- Lateral geniculate body:** **Visual** "Lateral for Looking (visual)!"
- Medial geniculate body:** **Auditory** "Medial for Music (auditory)!"

Epithalamus

- Pineal body
- Paraventricular nuclei-anterior and posterior (NOT the same as hypothalamic nuclei)
- Posterior commissure Habenular nuclei
- Habenular commissure
- Stria medullaris thalami

Fields of Forel

These are myelin rich regions of the **subthalamus-pallidothalamic** fibres.

- H (or H3) Field of Forel:** **Prerubral** field
- H1 field of Forel:** **Thalamic** fasciculus
- H2 field of Forel:** **Lenticular** fasciculus

Hypothalamus

- Hypothalamus weighs only **4 grams** and forms **0.3% of brain weight** BUT its functions are very significant- it is also known as '**head ganglion**' of the autonomic nervous system.
- Hypothalamic regions and nuclei in them are mentioned below.

Region	Nucleus/nuclei
Preoptic region	Preoptic nucleus
Supraoptic region	Supraoptic nucleus Anterior nucleus Paraventricular nucleus
Tuberal region	Arcuate nucleus Ventromedial nucleus Dorsomedial nucleus Lateral nucleus
Mammillary region	Posterior nucleus Mammillary nuclei

Functions of Hypothalamus are:

- General autonomic effects
 - Anterior hypothalamus** mediates **Parasympathetic** activity
 - Posterior hypothalamus** mediates **Sympathetic** activity ("APPS")
- Neurosecretion
 - Oxytocin** (paraventricular nucleus)
 - Vasopressin** (supraoptic nucleus)
 - These are secreted by hypothalamus and transported to the posterior pituitary.
- Temperature regulation**
 - Anterior hypothalamus** prevents rise in body temperature.
 - Posterior hypothalamus** promotes heat conservation and heat production when cold (**shivering** center)
- Appetite regulation**
 - Lateral feeding centre** responsible for Hunger - destruction can cause anorexia and starvation

- Ventromedial satiety centre** - destruction can cause hyperphagia and obesity.
- Lateral hypothalamus** also acts as **thirst center**.
- Thirst and water balance** (supraoptic nucleus).
- Sexual behaviour, emotion, fear** (Septal nucleus - destruction can cause rage).
- Circadian rhythm maintenance** (**biological clock** - **suprachiasmatic nucleus**).
- Endocrine control** (by forming releasing hormones e.g. TRH, CRH etc...)

MIDBRAIN

Parts of midbrain are midbrain, pons and medulla oblongata.

Midbrain

- Midbrain connects the **pons and cerebellum** to the **diencephalon**. Its cavity is the **cerebral aqueduct of Sylvius** which connects the 3rd ventricle with 4th ventricle.
- Parts of midbrain are:
 - Tectum** (roof of midbrain), lies posterior to cerebral aqueduct; it consists of two superior + two inferior colliculi (**corpora quadrigemina**).
 - Cerebral peduncle** located anterior to cerebral aqueduct. Each peduncle is subdivided into (a) **crus cerebri** anteriorly (b) **substantia nigra** in the middle and (c) **tegmentum** posteriorly.
- Grey matter in midbrain includes the **red nucleus**, **substantia nigra**, the **cranial nerve nuclei of III and IV** and a portion of the large sensory nucleus of V (**mesencephalic nucleus** containing **pseudounipolar** neurons similar to those of **sensory ganglia**).
- Fibres in the crus cerebri** are
 - Medial part-frontopontine fibres
 - Middle part-corticospinal + corticonuclear (cortico-bulbar) fibres
 - lateral part-temporopontine, parietopontine and occipitopontine fibres.
- Ascending sensory fibres** travel in the **lateral and medial lemnisci**.
- Descending motor fibres** pass en route to pons and spinal cord.
- The **superior colliculi** form the **rostral two bumps** (one on each side) on the **dorsal aspect of the midbrain**; the **caudal two bumps** are the **inferior colliculi**.
- Superior colliculus** is a **VISUAL** reflex center; **inferior colliculus** is an **AUDITORY** structure. ("Superior= Vision; Inferior = Hearing-Eyes are above the ears'!)

Pons

- Pons means '**bridge**'.
- Lies between the medulla and midbrain and is connected to the **cerebellum** by the **middle cerebellar peduncle**.
- Upper pons**: most prominent features are the pontine nuclei and the pontocerebellar fibres anteriorly.
- Lower pons**: dorsal surface forms the upper part of the floor of the fourth ventricle.
- Contains the **nuclei of the VI, VII and VIII** cranial nerves. (The **sensory nucleus of V** is extensive, extending from the midbrain to the upper cervical level, with the **most important part in the pons and the medulla**).
- The **motor nucleus of V cranial nerve** is in the pons.
- The corticospinal tracts cross in the lower pons.
- Abducens (VI) nucleus** underlies the **facial colliculus**.
- Superior and inferior salivatory** nucleus, and **lacrimatory** nucleus lie just above the ponto-medullary junction.

Medulla Oblongata

- Continuous through the foramen magnum with the spinal cord, and above with the pons.
- Connected to the **cerebellum** by the **inferior cerebellar peduncle**.
- The **olive** overlies the large inferior olivary nucleus.
- Contains the **nucleus ambiguus** (motor to IX, X and XI) and the **nucleus solitarius** (sensory to VII, IX and X).
- Most prominent cranial nerve nuclei** are IX, X, XI and XII.
- Other prominent features are decussation of **corticospinal (pyramidal)** fibres; nucleus **gracilis** and nucleus **cuneatus**.
- The **dorsal column nuclei** cross to form the **medial lemniscus**.
- Vital point**: The point in the medulla close to the floor of the fourth ventricle, the puncture of which causes instant death due to destruction of the respiratory center.

Blood

- Anterior Spinal artery**: supplies Medial region; thrombosis leads to "**Medial medullary syndrome**" [see more in CNS chapter (Pg 779)]
- Posterior Inferior Cerebellar artery (PICA)**: supplies posterolateral region; thrombosis leads to "**Lateral medullary (Wallenberg or PICA) syndrome**" [see more in CNS chapter (Pg 779)]
- Posterior spinal artery**: supplies posterior region.
- Remember!-All the three arteries mentioned above are branches of the vertebral artery.

CEREBELLUM

- It is situated in the *posterior cranial fossa* behind the pons and medulla. Its weight is about **150 grams**.
- Each hemisphere is divided into **three lobes**-(*anterior, middle* and *flocculonodular* lobes) with the help of two fissures-primary fissure (*fissura prima*) and *postero-lateral* fissure (*first fissure* to appear during development).
- The *flocculonodular lobe* is the **smallest lobe**.
- There are 4 pairs of *intra-cerebellar* or *deep cerebellar* nuclei from *lateral to medial* side ("DEFG"):
 - Nucleus Dentatus (largest)
 - Nucleus Emboliformis,
 - Nucleus Fastigii and
 - Nucleus Globosus.
 - Nucleus emboliformis and globosus are sometimes referred together as "*nucleus interpositus*".
- Histology** of cerebellar cortex-3 layers
 1. Molecular layer: *stellate* and *basket* cells
 2. Middle layer: *Purkinje* cells only
 3. Granule cell layer: *granule* cells and *Golgi* cells.
 - Cerebellum has **largest population of inhibitory neurons** in the CNS
 - ONLY **excitatory** neuron in cerebellum is *granule cell*.
 - ONLY output of cerebellar cortex is via *Purkinje cell axons*.
 - Inputs to cerebellum is via *mossy fibres* (major input from all parts of body and also cerebral cortex) and *climbing fibres* (from *inferior olivary nucleus*).
- Cerebellar peduncles**: There are 3 cerebellar peduncles which connect the cerebellum to the brainstem: *midbrain* (*superior*); *pons* (*middle*) and *medulla* (*inferior cerebellar peduncle*).
 - Superior cerebellar peduncle is Chiefly Efferent; BUT Middle and Inferior are chiefly Afferent (SE-MIA)
 - Superior cerebellar peduncle: Only *afferent* tracts are *anterior spinocerebellar*, *tectocerebellar*.
 - Middle cerebellar peduncle: ONLY *afferent-pon-tocerebellar* tract.
- Blood supply of cerebellum**
 - Superior cerebellar artery (from basilar A)
 - Anterior inferior cerebellar A (AICA-from basilar A)
 - Posterior inferior cerebellar A (PICA-from vertebral A)

Phylogenetic Divisions of Cerebellum

Archl-cerebellum (vestibulo-cerebellum)

- Most **primitive** parts of the cerebellum.
- Nucleus *Fastigius* Consist of *lingula* and *flocculonodular lobe*.
- Mainly concerned with **balance and maintaining equilibrium**.
- Coordinates movements of eyes with head movements (*vestibulo-ocular reflex*)

Paleo-cerebellum (spino-cerebellum)

- Consist of entire anterior lobe except the - *lingula*, the *pyramids* and *uvula* of the posterior lobe.
- Emboliformis* and *glabrous* nuclei Mainly concerned with maintaining **tone and posture** of the body.
- Smaothens* and coordinates **ongoing movements**.

Neo-cerebellum (cerebra-cerebellum)

- Most **recent part** of the cerebellum.
- Consists of middle lobe without *pyramid* and *uvula*.
- Mainly concerned with **planning and programming / fine tuning of voluntary movements**
- Dentate* nucleus

EXTRA EDGE

- Tracts inputting to the cerebellum with **proprioceptive** inputs are: *alivacerebellar* tract, *spinocerebellar* tract and *cuneocerebellar* tract.
- Tectocerebellar* tract gives **visual and auditory** inputs.

BASAL GANGLIA

- Lentiform* nucleus (*putamen + globus pallidus*)
- Caudate* nucleus
- Amygdaloid* nuclear complex
- Claustrum*
 - Also know that *corpus striatum* = caudate + lentiform nucleus.
- The below two masses of grey matter are closely related functionally to the basal ganglia
 - *Substantia nigra*
 - *Subthalamic nucleus*
- Functions of basal ganglia:
 - Controls the process by which and **abstract thought is converted to voluntary action**-i.e, the **initiation, planning, programming and smoothening** of movement.

CRANIAL NERVES

Location of Cranial Nerve Nuclei

Located in tegmentum portion of brainstem (between dorsal and ventral pons)

- Midbrain : Nuclei of CN III, IV
- Pons : Nuclei of CN V, VI, VII, VIII
- Medulla : Nuclei of CN IX, X, XI, XII

Functional Aspects of Cranial Nerve Nuclei

- General Somatic Efferent** nuclei: CN supplying *skeletal muscles* of somatic origin: **III, IV, VI, X**.
- General Visceral Efferent** nuclei: CN carrying *parasympathetic fibres*; these nuclei give origin to *preganglionic fibres* that constitute the *cranial parasympathetic outflow*-postganglionic fibres supply *smooth muscles or glands*: **III, VII, IX, X**
- Special Visceral Efferent** nuclei: A.k.a *Branchial efferent* or *branchiomotor nuclei*; they supply *skeletal muscles derived from branchial arches*; it includes:
 - Motor nucleus of *trigeminal nerve*
 - Nucleus of *facial nerve*
 - *Nucleus ambiguus*: lies posterior and lateral to the inferior olive in the *medulla*. Inferiorly it is continuous with the *spinal accessory nucleus*; it contributes fibres to the **IX, X and XI nerves**.
- General and Special Visceral Afferent** nuclei: It includes:
 - *Nucleus of tractus solitarius*: lies in the **lower medulla**; its upper part receives **taste** sensation through **VII, IX and X** nerves; its lower part receives **general sensations** from viscera.
- General Somatic Afferent** nuclei: this is represented by the **three sensory nuclei of trigeminal nerve** (main/superior sensory nucleus; spinal nucleus and mesencephalic nucleus). It receives touch, pressure, pain, temperature from face and proprioceptive impulses from muscles of mastication.
- Special Somatic Afferent** nuclei: includes **vestibular and cochlear** nuclei.

- Putamen circuit* is involved in subconscious execution of learned patterns of **skilled movement** (ex: cutting paper with scissors, hammering a nail, passing a basketball through a hoop etc.).

LIMBIC SYSTEM

- Limbic system is concerned with **emotional** behaviour, **sexual** behaviour and **food** habits. (The famous **5 F's**: *Feeling, Fighting, Fleeing, Feeding* and *sex*).
- Constituents of limbic system are:
 - Cortical grey matter
 - Limbic lobe: *uncus*, *parahippocampal* gyrus and *cingulate* gyrus
 - Hippocampal formation: hippocampus, dentate gyrus, gyrus fasciolaris and induseum griseum
 - Subcortical grey matter:
 - Dorsomedial nucleus of thalamus
 - Anterior nucleus of thalamus
 - Amygdaloid complex
 - Hypothalamus (including mammillary bodies)
 - Septal nuclei
- Interconnecting fibre tracts of limbic system

Papez circuit

- Hippocampus → mammillary body → anterior nucleus of thalamus → cingulate gyrus → entorhinal cortex → back to hippocampus.

More High Yield Points

- Structures found in the **floor of the third ventricle** from before backwards are:
 - Optic chiasma
 - Tubercinerium and infundibulum
 - Mammillary bodies
 - Posterior perforated substance
- The **calcar avis** (earlier called hippocampus minor) is an involution on the lateral ventricle's posterior horn produced by the calcarine fissure.

Nerve	CN	Function	Type	Mnemonic
Olfactory	I	Smell	Sensory	Some
Optic	II	Vision and light reflexes (direct and consensual)	Sensory	Say
Oculomotor	III	Ocular movement, pupil constriction (sphincter pupillae), accommodation (ciliary muscle), eyelid opening (levator palpebrae superioris)	Motor	Marry
Trochlear	IV	Ocular movement - superior oblique	Motor	Money

Contd...

Contd...

Nerve	CN	Function	Type	Mnemonic
Trigeminal V1: Ophthalmic and V2: Maxillary (pure sensory) V3: Mandibular (mixed nerve)	V	Mastication, facial sensation	Both	But
Abducens	VI	Ocular movement – lateral rectus	Motor	My
Facial	VII	Supplies Muscles of facial expression Taste from anterior 2/3 of tongue, Secretomotor: lacrimal gland (lacrimation), salivation (submandibular and sublingual glands, NOT parotid), nasal glands Eyelid closing (orbicularis oculi), Stapedius muscle in ear	Both	Brother
Vestibulocochlear	VIII	Hearing, balance, position of head	Sensory	Says
Glossopharyngeal	IX	Taste from posterior 1/3 of tongue, swallowing, salivation (parotid), monitoring carotid body and sinus chemo and baro-receptors, and stylopharyngeus	Both	Big
Vagus	X	Taste from epiglottic region, swallowing, palate, elevation, talking, coughing, thoracoabdominal viscera, monitoring aortic arch chemo and baro-receptors.	Both	Brains
Accessory Cranial (smaller) Spinal	XI	Head turning (sternocleidomastoid); shoulder shrugging (trapezius) The cranial part of accessory nerve joins the vagus and is distributed through the vagus to pharyngeal, palatal and laryngeal muscles	Motor	Matter
Hypoglossal	XII	Tongue movement, Unilateral hypoglossal nerve injury: Tongue undergoes hemiatrophy; affected side shows fasciculations; tongue deviates towards side of lesion on protrusion. If bilateral, tongue protrusion is NOT possible and patient can have dysphagia.	Motor	Most

In the above mnemonic the B's also give the Branchial arch nerves in order:

• But (CN V, Trigeminal, Mandibular)	: 1st arch
• Brother (CN VII, Facial)	: 2nd arch
• Big (CN IX, Glossopharyngeal)	: 3rd arch
• Brains (CN X, Vagus)	: 4th arch

MUST Know MCQ facts about Cranial Nerves

Only CN without thalamic relay to cortex; CN which enters cerebrum directly	Olfactory (CN I)
Thinnest/most slender and smallest CN	Trochlear (CN IV)
ONLY CN. that emerges from the brainstem on its dorsal aspect	
CN with longest Intracranial course (subarachnoid)	
CN with least number of fibres and completely decussates before reaching its target	
Nerve arises from contralateral nuclei (i.e., right trochlear nerve arises from left trochlear nucleus and vice versa)	
Thickest/Largest CN	Trigeminal nerve (CN V)
Largest branch of trigeminal nerve	Mandibular nerve
Trigeminal nerve has 4 nucleus	3 sensory and 1 motor
The only sensory ganglion located inside the cranial cavity is	Trigeminal ganglion

Contd...

Contd...

MC affected CN with raised intracranial pressure due to long Intracranial course – false	Abducent nerve (CN VI)
localizing sign	
MC CN affected in spinal anesthesia	
CN nucleus lying deep to facial colliculus	
CN passing through Dorello's canal at petrous apex	
CN with longest Intradural course	
CN with longest Intraosseus course	Facial nerve (CN VII)
MC injured motor CN	
Cranial nerve nuclei in relation to the floor of the fourth ventricle	VI, X, XII
Only muscle supplied by glossopharyngeal nerve (CN IX)	Stylopharyngeus
first branch of facial nerve	Greater petrosal nerve
first branch of vagus	Auricular nerve (Alderman's nerve)
CN with longest extracranial course	Vagus (CN X)

More Info about Cranial Nerves Supplying the Eye

- In Oculomotor nerve (CN III)
 - The two medial subnuclei innervate the contralateral superior rectus.
 - The median caudal subnucleus provides bilateral innervation (i.e, it innervates both right and left levator palpebrae superioris.
- Each Trochlear nerve (CN IV) innervates the contralateral superior oblique.
- Trochlear nerve was also called 'pathetic nerve' due to the dejected appearance of patients with superior oblique palsies!.
- Each Abducent nerve nucleus (CN VI) has axons supplying ipsilateral lateral rectus muscle and ALSO has axons which terminate in the contralateral oculomotor nucleus (supplies medial rectus)-this is to ensure that simultaneous contraction of ipsilateral lateral rectus and contralateral medial rectus muscles occur during horizontal movements of the eyeball !

Cranial Nerve Reflexes

Cranial nerve reflex	Afferent	Efferent
Corneal	V-1 (Ophthalmic)	VII
Lacrimation	V-1	VII
Jaw jerk	V-3, mandibular (sensory)	V-3 (motor)
Pupillary	II	III
Gag	IX	IX, X

BLOOD SUPPLY OF BRAIN

- Right common carotid A. arises from the Brachiocephalic A.
- Left common carotid A. arises from the Aortic arch.

- Each common carotid A. divides at the level of the upper border of the thyroid cartilage (C4 level) into internal carotid and external carotid A. At this bifurcation carotid body and carotid sinus are present.
- Carotid body has chemoreceptors and monitors the oxygen partial pressure.
- Carotid sinus has baroreceptor and it monitors blood pressure.
- Brain is supplied by branches of the two internal carotid and two vertebral arteries.

Internal Carotid Artery

- Enters skull via the carotid canal. In carotid canal it is surrounded by a plexiform sheath of postganglionic fibres.
- Branches of Internal carotid artery are:
 1. Cervical part: no branch arises from internal carotid A. in the neck.
 2. Petrous part: caroticotympanic and pterygoid branch.
 3. Cavernous part: Branch to trigeminal ganglion, superior and inferior hypophyseal branches (to pituitary).
 4. Cerebral part:
 - Ophthalmic A.: accompanies optic N. and gives following branches:
 - Central retinal A.
 - Supra-orbital artery
 - Long and short posterior ciliary arteries
 - Anterior and Posterior ethmoidal artery
 - Medial palpebral artery
 - Muscular arteries
 - Two terminal branches: Dorsal nasal artery and Supratrochlear artery.

➤ **Anterior cerebral A.** Supplies the medial surface of the frontal and parietal cortex (medial surface of brain), leg-foot area of motor and sensory cortices. Its branches are:

- **Recurrent branch of the anterior cerebral A.** (A. of Huebner) enters the anterior perforated substance.

➤ **Middle cerebral A.** Supplies greater part of superolateral surface of brain, auditory area, trunk-arm-face area of motor and sensory cortices.

- **Lateral striate branch** - "artery of stroke, Charcot's Artery of Cerebral Haemorrhage" supplies internal capsule, caudate, putamen, globus pallidus.

➤ **Posterior communicating A.**: common area of aneurysm that causes CNIII palsy.

➤ **Anterior choroidal A.** Enters inferior horn of lateral ventricle through choroidal fissure.

Circle of Willis

- **Posterior communicating artery** anastomoses with the **posterior cerebral A.** The internal carotid and verteobasilar system are connected by Posterior communicating A. Ant. cerebral A. of two sides are connected by the **Ant. communicating A.** As a result of these anastomoses an arterial circle (**Circle of Willis**) is formed.

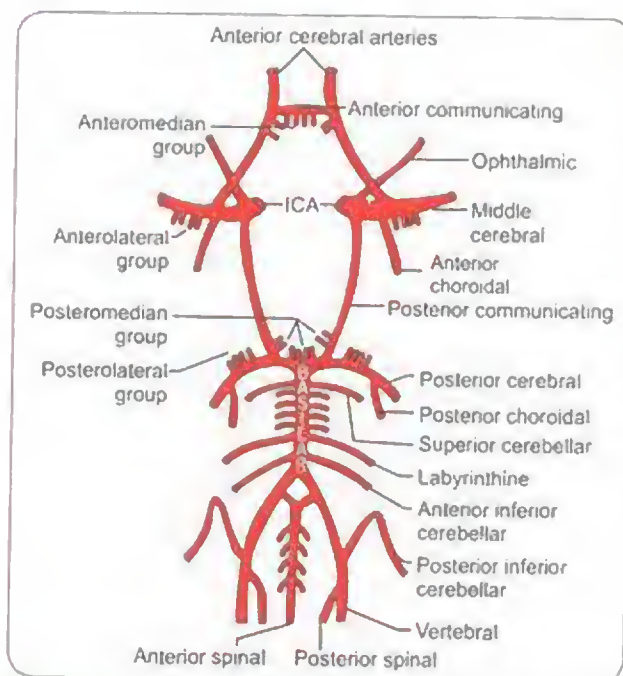


Fig. 2.79: Circle of Willis and intracranial branches of internal carotid and verteobasilar arteries

Berry Aneurysms

- Berry aneurysms occur at the bifurcations in the circle of Willis.
- **MC site is bifurcation of the anterior communicating artery.**
- Rupture leads to **hemorrhagic stroke/Subarachnoid hemorrhage.**
- A/w ADPKD, Ehlers Danlos syn., Marfan's syn.. Other risk factors: advancing age, hypertension, smoking race (higher risk in blacks)

External Carotid A.

- Each common carotid A. divides at the level of the **upper border of the thyroid cartilage (C4 level)** into internal carotid and external carotid A.
- Branches of external carotid artery are:
 - Superior thyroid A.
 - Ascending Pharyngeal A. (*smallest branch*)
 - Lingual A.
 - Facial A.
 - Occipital A.
 - Posterior auricular A.
 - Superficial temporal A.
 - **Maxillary A. - Middle Meningeal A.** is an important branch of this.

Mnemonic: "Sad And Lonely Fellow Omitted (to read) PSM!"

Vertebral A.

- It arises from **first part of Subclavian A.** It runs through the **transverse foramina of the upper 6 cervical vertebrae.** It then **enters the vertebral canal**
- Branches of vertebral artery are:
 - Spinal, Muscular and meningeal branches.
 - **Posterior Inferior Cerebellar A (PICA)**- **largest branch.** Sometimes, it gives off the posterior Spinal A.
 - **Anterior Spinal A.** - is a single artery; it is present in the **anterior median fissure.**
 - **Posterior Spinal A** - There are **two** (one on each side); may sometimes arise from the vertebral A.
 - **Basilar A.** - At the lower border of the pons **Vertebral A. unites with its fellow** of the opposite side to form the Basilar A. Basilar artery in turn ends at upper border of pons by dividing into the right and left Posterior Cerebral A. Branches of vertebral artery are:
 - **Posterior cerebral A.**—terminal branches.
 - **Anterior inferior cerebellar A.**
 - **Labyrinthine A.**- BUT more commonly this arises from Ant. Inferior Cerebellar A.
 - Superior cerebellar A.
 - Pontine A.

EXTRA EDGE

- **Oculomotor nerve** leaves the midbrain by passing **between** 2 major branches of the basilar artery—the **posterior cerebral and superior cerebellar artery.**

CAVERNOUS SINUS

- Cavernous sinus is a collection of venous sinuses on either side of the pituitary.
- Blood from eye and superficial cortex → cavernous sinus → internal jugular vein
 - Structures passing through wall of cavernous sinus:
 - **CN III,**
 - **CN IV,**
 - **CN V-1 (Ophthalmic N) and V-2 (Maxillary N)** and
 - **Postganglionic sympathetic fibres** en route to orbit all pass through the **wall of cavernous sinus**
- **NOTE:** **CN VI** and **internal carotid artery** are '**free floating**' inside cavernous sinus and closely related to the floor

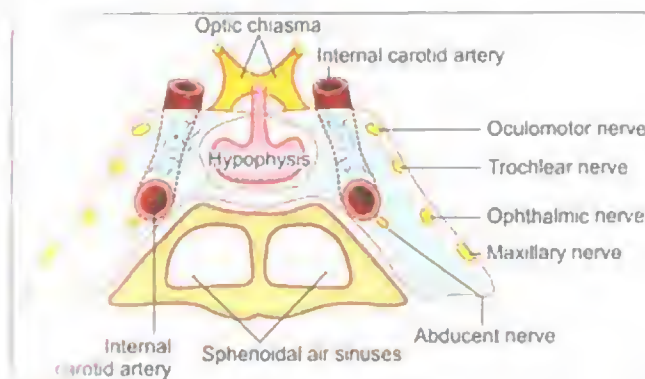


Fig. 2.80: Relations of cavernous sinus

Cavernous Sinus Thrombosis

- **Etiology:**
 - Infections in dangerous area of face (**Nasal furuncles MC**) spreads through **superior and inferior ophthalmic vein.**

➤ **Sphenoidal or ethmoidal sinusitis,**

➤ Others: dental infections, spread from other cranial venous sinuses

➤ **Staphylococcus aureus** (70%), is the MC pathogen.

• **Clinical features:**

➤ MC symptom: **headache.**

➤ Classical triad Uncludes abrupt onset of **unilateral or bilateral progressive chemosis, periorbital edema, proptosis** and **photophobia.**

➤ Other signs: Prosis, Cranial nerve palsies (III, IV, V, VI). **CN VI palsy is the MC.**

➤ **Sensory deficits** of the **ophthalmic and maxillary branch of the fifth nerve** are common. Periorbital sensory loss and impaired corneal reflex may be noted.

➤ **Papilledema, retinal hemorrhages, and decreased visual acuity** and blindness may occur from venous congestion within the retina.

➤ **Appearance of signs and symptoms in the contralateral eye is diagnostic of CST,** although the process may remain confined to one eye.

➤ Fever, tachycardia, sepsis may be present. Headache with nuchal rigidity may occur.

➤ Pupil may be dilated and sluggishly reactive.

➤ **Infection can spread to contralateral cavernous sinus** within 24-48 hr of initial presentation.

• **Inv. of choice** is **MRI** with contrast and **MRV.**

• **Treatment:** includes **high dose IV antibiotics** (rarely corticosteroids).

• **Surgical drainage** is indicated if **sphenoid sinus involvement** present

Few important names in cerebral venous drainage

- Superficial cerebral veins include:
 - Superior anastomotic vein (of Trolard)
 - Inferior anastomotic vein (of Labbe)
- Deep cerebral veins include:
 - Great cerebral vein (of Galen)
 - Internal cerebral veins
 - Basal vein (of Rosenthal)

MORE ANATOMY MCQ TOPICS

Named Nerves

- **Nerve of Bell:** Long thoracic N. (nerve to serratus anterior).
- **Arnold's nerve** or **Alderman's nerve:** Auricular branch of Vagus.
- **Nerve of Jacobson:** Tympanic branch of glossopharyngeal nerve (9th).

- **Nerve of Latarjet:** Branch of anterior gastric nerve supplying the pylorus; It is **left intact in highly selective vagotomy** so that the function of gastric emptying remains intact
- **Vidian Nerve:** Nerve of pterygoid canal.
- **Nerve of Wrisberg:** Sensory component of facial nerve (carries taste sensation from the anterior 2/3 of tongue and general sensation from external auditory canal).

- **Criminal Nerve of Grassi:** A branch of the right posterior vagus which passes to the left behind the oesophagus, ending in the gastric cardia; it *should be cut and dissected in highly selective vagotomy* to avoid recurrent peptic ulceration.
- **Wandering/vagabond nerve:** Vagus

History of Anatomy

- **Hippocrates:** *Father of Medicine* and founder of anatomy.
- **Herophilus:** First to perform *dissection of human body in public*.
- **Mondino:** Wrote a *book of anatomy called Anothomia*.
- **Andreas Vesalius:** *Father of "modern anatomy"*
- **William Harvey:** Discovered *circulation of blood*.

C H A P T E R

3

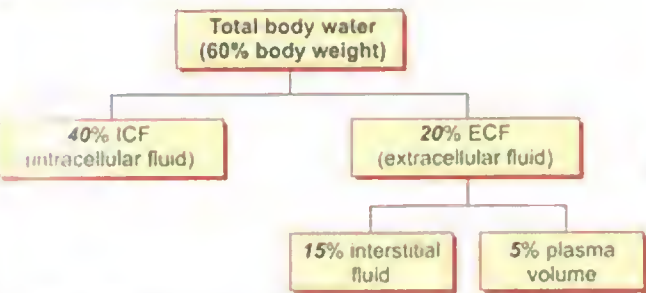
Physiology

BODY FLUID PHYSIOLOGY

In an average 70 kg man

Body weight %	Substance
60% (42 kg/42 L)	Water
17% (12 Kg)	Protein
15% (13 Kg)	Fat
4% (3 Kg)	Minerals
Fat free mass (lean body mass)	70-13 = 57 Kg
Out of 12 kg of protein	Skeletal muscle = 4 kg; Nonskeletal muscle = 8 kg

Body Water Distribution



- TBW = Total body water.
- *Intracellular fluid, ICF* = TBW - ECF;
- *Interstitial fluid volume* = ECF - Plasma volume.
- *total blood volume* = 8% of body weight = Plasma volume (5%) + Volume of RBCs (hematocrit, 3%).
- *total Blood volume* = Plasma volume/(1-hematocrit)
- *transcellular fluid* includes fluid in the synovial, pericardial, peritoneal, pleural and intraocular spaces and CSF also accounts for 1-3% of body weight (1-2 L).
- *Basic physiologic water requirement* for survival of an individual is 2 litres/day.

Measurement of Body Fluid Volumes

- The volume of various body fluids is calculated by *indicator dilution* method.

- Substances used for measurement of fluid compartments are as in table below:

Fluid volume	Indicator/Dye used
Total body water (TBW)	D ₂ O (deuterium oxide) MC used; tritium oxide and antipyrine also used.
Extracellular fluid (ECF)	Inulin (most accurate) , sucrose, mannitol, sodium thiosulfate, sodium iothalamate
Plasma volume	Evans blue (T-1824); ¹²⁵ I- Albumin (MC used)
RBC volume	Tagging RBCs with ⁵¹ Cr, ⁵⁹ Fe, ³² P

EXTRA EDGE

- Graphical (diagrammatic) representation of body fluid compartments is by **Darrow-Yannet diagram**
- Main ions in **ECF:** **Na⁺** (most abundant cation); **Cl⁻**; **HCO³⁻**; **Ca²⁺**
- Main ions in **ICF:** is **K⁺** (most abundant cation); Mg²⁺, organic anions (phosphate, protein)
- Mnemonic: ("**E-NIK**.....NOT...Nike!").

TRANSPORT ACROSS CELL MEMBRANES

Active vs Passive Transport

Active transport	Passive transport
Against electrochemical gradient ('Uphill')	Along the gradient ('downhill')
Energy (ATP) required	No energy required
Exhibits saturation kinetics	May not be required
Examples Primary active transport Secondary active transport	Examples Simple diffusion Facilitated diffusion Osmosis Filtration Bulk flow Solvent drag

Carrier Mediated Transport

- Carrier mediated transport includes
 - **Facilitated diffusion**
 - **Primary and secondary active transport.**

- Unique features are:

- **Competitive inhibition:** Structurally related solutes compete for transport sites on carrier molecules. (Example: galactose is a competitive inhibitor of glucose transport in the small intestine).
- **Saturation kinetics:** The transport rate increases as the concentration of the solute increases and reaches a transport maximum (T_{max}) until the carriers are saturated.

Types of Carrier Proteins

- **Uniport:** the carrier protein transports *only one substance*; e.g. Na^+ channel transports only Na^+ and K^+ channel transports only K^+ .
- **Symport (Co-transport):** Symport carrier transports *two or more substances* from one side of the membrane to the other in the *same direction*. Example: **Glucose and amino-acids** are transported along with **sodium** from the lumen of intestine or kidney into epithelial cells.
- **Antiport:** Carriers transport substances in *opposite directions (counter-transport)* - in which one substance is transported to the inside of the cell and other substance from inside to outside. Examples are:
 - **Na^+-K^+ pump:** Discussed in detail below under primary active transport.
 - **Na^+-H^+ exchanger** in proximal tubular cells of nephron; inward diffusion of Na^+ is coupled with outward diffusion of H^+ .

Simple Diffusion

- Simple diffusion is a **passive** transport in which molecules move from area of higher concentration to area of lower concentration.
- Examples of simple diffusion are O_2/CO_2 exchange in alveoli; urea and ammonia in kidney tubules; ion exchanges etc.
- Simple diffusion follows **Fick's law of diffusion as given below.**

$$J = -DA/TX(CI - CO)$$

- J = Net rate of diffusion
- D = Diffusion coefficient
- A = Area
- T = Thickness of the membrane
- CI and CO = Concentration of substance Inside and Outside the cell.
- The "minus" sign indicates the direction of diffusion; for diffusion from higher to lower concentration, the sign is negative.

Facilitated Diffusion

- Also called '**carrier mediated diffusion**' since diffusion is facilitated by a **carrier protein in the membrane**.
- It is also a **passive** transport.
- Examples: Transport of various sugars into red cells, adipose tissue, skeletal and cardiac muscles.
- Differences between simple and facilitated diffusion are given below:

	Simple diffusion	Facilitated diffusion
Mode of Diffusion	No carrier molecule involves	Carrier molecule involved
Saturation Kinetics	No saturation kinetics	Has saturation kinetics; no increase in diffusion once saturation is reached
Competitive inhibition	Absent	Substances that share the same carrier compete for transport
Rate of diffusion	Maybe slow	Faster
Specificity	No specificity	Carrier protein maybe specific

Non-Ionic Diffusion

- In case of **weak acids/bases**, where the acid/base can cross the membrane in the non-ionised form but cannot cross the membrane in the ionised form.
- Example: **Ammonia** transport in the GIT/Kidneys.

Osmosis

- Osmosis is the **passive** process of movement of solvent (water) from the solution with **low solute concentration** to the solution with **high solute concentration** when both solutions are separated by a **semi-permeable membrane**. (Or from solution with **higher thermodynamic water activity** to solution with **lower thermodynamic water activity**).
- A substance to maintain a stable osmotic pressure should be **confined to one side** of the membrane.
- Thus **plasma protein is osmotically most effective** since it is neither transferred from nor metabolized in the compartment.
- But **urea and glucose** are **osmotically ineffective!** (Since urea can diffuse readily across cell membrane cannot impart sustained osmotic effect and glucose is metabolised easily in the blood).

- Osmolality:** Is the number of particles (osmoles) of solute dissolved in one kg of solvent/water. (i.e. mOsmol/kg).
- The **freezing point of normal human plasma is -0.54°C** , which corresponds to an osmolal concentration in the plasma of 290 mOsm/Kg = **normal plasma osmolality**.
- Tonicity:** Osmolality of a solution relative to plasma; 0.9% NaCl and 5% dextrose are isotonic to plasma.
- Osmolarity:** Is the number of particles dissolved in a litre of solution (i.e. mOsmol/l).

EXTRA EDGE

- The main factor **promoting filtration** is **capillary hydrostatic pressure**.
- The main factor **promoting absorption** is **plasma protein osmotic force**.
- The **most important buffer** system in the plasma is **bicarbonate buffer** system.

Osmotic Pressure

- Osmotic pressure** is the minimum pressure applied to the solution with higher solute concentration to prevent osmosis.
- 1 gram molecular weight** of any substance exerts osmotic pressure = **22.4 atmospheres**.
- The **colloid osmotic pressure** due to colloidal particles in plasma (plasma proteins, especially **albumin**) is called the **oncotic pressure**. The normal oncotic pressure is **25 mmHg**.
- Calculating osmotic pressure is by **Van't Hoff's law**

$$p = g \times CRT$$
 - p = osmotic pressure (mm HG or atm)
 - g = number of particles in solution (mOsmol/l)
 - R = gas constant
 - T = absolute temperature (K)

Other Transport Phenomena

- **Filtration:** Defined as the process by which fluid is forced through a membrane mainly because of the difference in hydrostatic and oncotic pressure on two sides.
- **Bulk Flow:** When filtration results in movement of greater quantity of water, the process is called bulk flow.
- **Solvent drag:** When a solvent is moving in one direction, it tends to drag along some molecules of solute.

Primary Active Transport

- In primary active transport, the energy is derived directly from hydrolysis of **ATP**. This mechanism is operated by **ion pumps (ATPases)**.

- Features of **primary and secondary active transport** are as for "active transport" summarized in the table "Active vs Passive transport" above.
- Examples of ion pumps/ATPases are $\text{Na}^+ \text{K}^+$ ATPase; Calcium ATPases; $\text{H}^+ \text{K}^+$ ATPase and H^+ -ATPase.

1. $\text{Na}^+ \text{K}^+$ pump ($\text{Na}^+ \text{K}^+$ ATPase)

- MC pump** present in all parts of the body; operated by **$\text{Na}^+ \text{K}^+$ ATPase**.
- $\text{Na}^+ \text{K}^+$ ATPase is a **heterodimer** Consists of **3 alpha and 3 beta** subunits.
- At the **cytoplasmic side**, the **alpha subunit** has ATPase activity and binding sites for **3 Na^+ , ATP and phosphate**.
- At the **extracellular side**, **alpha subunit** has binding sites for **2 K^+ and ouabain**.
- Beta subunit** contains **3 extracellular glycosylation sites**, all of which attach **carbohydrate residues**.
- It actively **transports 3 Na^+ out of the cell**, and **2 K^+ into the cell** for each molecule of ATP hydrolyzed; i.e., coupling ratio is **3:2**.
- This pump is an "**electrogenic pump**" since it produces a net movement of positive charge out of the cell.
- This pump is **inhibited by ouabain** and related **digitalis glycosides**.

2. Ca^{++} Pump (Ca^{++} ATPase)

- Present in all cell membranes; membrane of endoplasmic reticulum and sarcoplasmic reticulum.
- The calcium pump **actively transports calcium out of the cell** and thus maintains a higher concentration of calcium in the **ECF (10^{-3} molar)** compared to inside the cell (10^{-7} molar) - meaning ICF calcium concentration is **10,000 times less than ECF**.

3. $\text{H}^+ \text{K}^+$ ATPase

- In **parietal cells of gastric glands** of stomach, it pumps proton into the gastric lumen in exchange for K^+ . This is the primary step in **HCl secretion** in the stomach.
- In **kidney**, it secreted H^+ into the tubular fluid and reabsorbs K^+ ; hence it plays an important role in acidification of urine.

ABC Transporters

- **ATP-Binding Cassette transporters.** Examples are
 - **MDR-1** protein (Multidrug resistance -1 protein)
 - **BRCP** (Breast cancer resistance protein)
 - **CFTR** protein (Cystic fibrosis transmembrane regulator protein).

Secondary Active Transport

- This represents a *combination of primary active transport and facilitated diffusion*.
- Typical example is *reabsorption of glucose from kidney tubule or intestine*. The carrier protein that transports Na^+ into the luminal cell also transports glucose in the same direction.

Vesicular Transport

Exocytosis

- Exocytosis is involved when secretory granules are extruded out of the cell. This requires *calcium*

Type	Carrier protein required	Energy required	Electrochemical gradient	Inhibition of Na^+-K^+ ATPase
Simple diffusion	No	No	Downhill (along)	No effect
Osmosis	No	No	Downhill	No effect
Facilitated diffusion	Yes	No	Downhill	No effect
Active transport	Yes	Yes	Uphill (against)	Inhibits transport

MEMBRANE POTENTIAL

Equations Used for Membrane Potential

- **Gibbs-Donnan effect:** In presence of a non diffusible ion, the diffusible ions distribute themselves so that at equilibrium, their concentration ratios are equal.
- The extra osmotic pressure in normal human plasma over and above that caused by dissolved proteins is due to *Donnan effect*
- **Nernst equation:** This gives the value of *equilibrium potential* or *isoelectric potential*. At equilibrium, the distribution of permanent ions across the membrane is asymmetric and an electric gradient exists, whose magnitude can be determined.

Resting Membrane Potential

- An electric potential exists across the membrane of all living cells with the *inside being negative* in relation to outside. At resting state this is called *resting membrane potential (RMP)*, also known as, *transmembrane potential*.
- Genesis of RMP
 - **Diffusion of K^+ out of cell:** This is the *most important* cause. The *most permeable ion* in resting condition of the cell is $\text{K}^+ \gg \text{Cl}^- \gg \text{Na}^+$.

and *energy*. It is also called *emicytosis* or *reverse phocytosis*.

- **Constitutive exocytosis:** Seen in almost all cells; also responsible for secretion of mucus by goblet cells.
- **Regulated exocytosis:** *Non-constitutive* exocytosis; this is major mechanism of rapid secretion of hormones, neurotransmitters and digestive enzymes.

Endocytosis

- **Phagocytosis** ('cell eating')
- **Pinocytosis** ('cell drinking')
- **Clathrin mediated endocytosis** (uses both *clathrin* and *caveolin*)

➤ **Na^+-K^+ -ATPase** maintains the RMP

➤ **Donnan effect** also maintains the diffusion gradient for K^+ .

- In *neurons*, the RMP is -70mV which is *close to* the equilibrium potential of K^+ *but* the value of RMP is *exactly same as* equilibrium potential of Cl^- .
- RMP is calculated using **Goldman-Hodgkin-Katz** equation.

Tissue	RMP (mV)
Neuron	- 70
Skeletal muscle	- 90
Cardiac muscle	- 90

EXTRA EDGE

- **Increase in ECF K^+ concentration (hyperkalemia)** causes RMP to become more positive (i.e., *decrease in magnitude of RMP - depolarisation*).
- **Decrease in ECF K^+ concentration (hypokalemia)** causes RMP to become more negative (i.e., *increase in magnitude of RMP - hyperpolarisation*).
- **Current** flowing through **voltage gated channels** can be measured by "*patch clamp*" recordings.

CELLULAR PHYSIOLOGY

CELL MEMBRANE (PLASMA MEMBRANE)

- Cell membrane is **7-10 nm** thick
- It is made up of **50% proteins; 45% lipids** and **5% carbohydrates**.
- The most widely accepted model of cell membrane is the **fluid-mosaic model** described by *Singer and Nicolson* in 1972.
- According to fluid mosaic model, cell membrane consists of **lipid bilayer** that contains *protein molecules in between*.
- **Lipids in cell membrane:**
 - Cell membrane lipids are **amphipathic** molecules, i.e., their *head/polar region* is **hydrophilic** and *tail/nonpolar region* is **hydrophobic**. These lipids are arranged such that the *tail ends are directed towards the center of the membrane* whereas, the head ends are directed towards the ECF (on the outside) and cytoplasm (on the inside).
 - Major lipids are **Phospholipids (25%)—Lecithin** (phosphatidylcholine).
 - Other lipids are **cholesterol, glycolipids** (gangliosides and cerebroside).
 - **Triglycerides** are NOT present.
 - **Sphingomyelins** in cell membranes are specifically found in *nervous tissue*.
- **Proteins in cell membrane**
 1. **Integral (transmembrane) proteins:** These span the *entire thickness* of the cell membrane.
 2. **Peripheral proteins:** Maybe *intrinsic* (present on inner surface of membrane) and *extrinsic* (present on outer surface).

Functions of cell membrane proteins

- | Integral proteins | Peripheral proteins |
|---|--|
| <ul style="list-style-type: none"> • Serve as channels (pores) • Act as carrier proteins (ex: glucose transporter) • Serve as ion pumps (ex: Na^+-K^+ ATPase) • Serve as receptors (membrane G proteins) • Antigenic proteins (ex: blood group antigens) | <ul style="list-style-type: none"> • Intrinsic proteins serve as enzymes or anchor proteins for cytoskeleton • Extrinsic proteins serve as cell adhesion molecules. |
- **Carbohydrates in cell membrane**
 - These are attached to proteins (glycoproteins) or lipids (glycolipids).

➤ Throughout the surface of the cell membrane, carbohydrate molecules form a thin loose covering called **glycocalyx**.

EXTRA EDGE

- The lipid bilayer of cell membrane acts as a **semipermeable** membrane; fat soluble substances like **alcohol, fatty acids and oxygen pass easily** but water soluble substances like **urea and glucose cannot** pass easily.

Effects of Temperature on Fluid Mosaic

- At lower temperatures, the hydrophobic chains of fatty acids are arranged in orderly fashion in *gel-like* state. When temperature increases to *transition temperature (T_m)*, the membrane becomes more *fluid-like*.
- Thus if T_m is higher, fluidity is low and vice versa.
- **Saturated fatty acid** chains interact strongly-thus cause **higher T_m = lower fluidity**.
- Similarly, **unsaturated fatty acid** chains (linoleic, linolenic acids)-cause **lower T_m -increased fluidity**.
- **Cholesterol** is the **key regulator** of membrane fluidity.

Dynamicity of Cell Membrane

- **Lateral diffusion** refers to the lateral movement of lipids and proteins found in the cell membrane. It is a **quick and spontaneous** process.
- **Transverse diffusion (flip-flop)** refers to movement of a lipid or protein from one membrane surface to the other (i.e., across the cell membrane); it is **extremely slow**.

Protein: Lipid Ratio of Biological Membranes

Membrane	Protein : Lipid ratio
Mitochondrial inner membrane	3.5:1 (Highest)
Plasma/cell membrane	1:1
RBC	1.25:1
Mitochondrial outer membrane	1.2:1
Nerve Myelin sheath	0.25:1 (lowest)

Marker Enzymes for Major Cell Organelle

Cell organelle	Enzymes
Mitochondria (inner membrane)	ATP synthase; Succinate dehydrogenase
Mitochondria (outer membrane)	Monoamine oxidase
Plasma membrane	5'-Nucleotidase; Na ⁺ -K ⁺ ATPase; Adenyl cyclase
Cytosol/Cytoplasm	Lactate dehydrogenase;
Golgi apparatus	Galactosyl or sialyltransferase
Endoplasmic reticulum	Glucosidase
Lysosomes	Acid phosphatase, Cathepsin, beta-glucuronidase
Peroxisomes	Catalase
Microsomes	Glucose-6-phosphatase

MITOCHONDRIA

- Mitochondria is called the 'powerhouse' of the cell since it contains the *enzymes for energy metabolism* and *ATP synthesis*.
- It has two components - *membranes* and *cristae*.
 - **Outer** mitochondrial membrane consists of *phospholipids* and *cholesterol* and contains specific membrane protein called "*porin*". Porin channels allow substances with molecular weight less than 10,000 to *freely diffuse* across the outer membrane.
 - **Inner** mitochondrial membrane is rich in *proteins*; ratio of *protein to lipid* is **3.5:1**; hence it is *impermeable to polar and ionic substances*. This inner membrane is folded into multiple septa called *cristae* which is rich in enzymes. Number of cristae is more in resting state and decreases in respiring state.
- **Mitochondrial matrix:** Region enclosed by inner membrane is called the matrix. *TCA (Kreb's) cycle* and *fatty acid oxidation* takes place in the matrix.
- **Enzymes in the inner membrane:** Cytochromes of the *electron transport chain* and associated enzymes (NADPH dehydrogenase)
- **Enzymes in the matrix:** enzymes of the TCA (Kreb's) cycle.
- As mitochondria have strands of *DNA*, they are capable of *self replication* as well as *protein synthesis*.
- **Large abundant abnormal mitochondria** in epithelial cells are called *oncocytes*-seen in *oncocytoomas*

ENDOPLASMIC RETICULUM (ER)

- **Largest organelle** of eukaryotic cell is *endoplasmic reticulum*
- The ER consists of a network of ahaatomosng *tubules, vesicles* and flattened *cisternae*.
- The membranes of ER are continuous with the *outer membrane of nucleus* and are also *connected with golgi apparatus*.
- **Rough** endoplasmic reticulum (RER) contains *ribosomes* attached to its cytoplasmic surface.
- Smooth Endoplasmic reticulum (SER) does not have ribosomes attached.
- **Ribosomes** are the *actual site of protein synthesis*. They contain **85% of RNA** of the cell.

Rough Endoplasmic Reticulum

- RER is involved in **synthesis of proteins**: Therefore RER is abundant in cells of endocrine glands (pancreas) and cells secreting digestive enzymes (goblet cells of intestines).
- RER is also involved in *co-translational modification of proteins* (including *N-linked glycosylation*; *hydroxylation* of proline and lysine during *collagen synthesis*).
- **Nissl bodies** (in neurons) are a modified RER.

Smooth Endoplasmic Reticulum

- SER is the site of **Steroid synthesis** (cholesterol, steroid hormones, phospholipids)
- It is also site for **detoxification of drugs/poisons**.
- In muscles it is called *sarcoplasmic reticulum* and is specialised for storage of *calcium ions*.
- Liver *hepatocytes* and *steroid producing cells of the adrenal cortex* are rich in SER.

GOLGI COMPLEX

- The **Golgi complex** (also known as *dictyosome*) is a stack of membranous cisternae and a *maturation site* located *close to the nucleus*.
- Anatomically and functionally it is closely related with *endoplasmic reticulum*.
- It is a **polarised structure** with the *cis face* (Ire region closer to the nucleus, *cis Golgi* - vesicle *receiving end*) and the *trans face* (region close to the membrane, *trans Golgi* - vesicle *secretory end*).
- Functions of golgi complex include:
 - **Post-translational modification** of proteins.
 - **Protein sorting and packaging** into *secretory granules*. *Secretory proteins* (e.g. insulin) are packaged

into *clathrin-coated vesicles*; *cell-membrane proteins* (e.g. hormone receptors) are packaged into *nonclathrin-coated vesicles*.

- It is the site for **incorporation of carbohydrates (glycosylation)** into newly synthesised proteins to form *glycoproteins*.
- Membrane recycling
- Lysosomal enzymes are formed in golgi apparatus

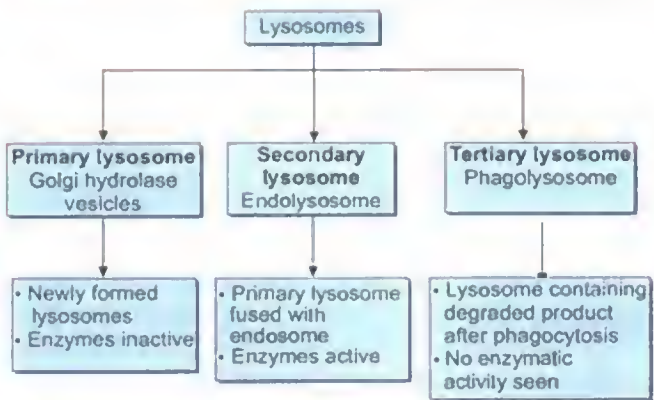
LYSOSOMES

- Lysosomes are membrane bound spherical organelle that contain **hydrolytic enzymes** (> 40 enzymes) for *intracytoplasmic digestion* of proteins, polysaccharides, fats and nucleic acids.
- Also known as "*suicidal bags* of cells".
- They are found in all cells *except RBCs*. Cells with *high phagocytic activity* (neutrophils, monocytes) have *abundant lysosomes*.
- The chief marker enzyme for lysosomes is **acid phosphatase**.
- The interior of the **lysosome is acidic (pH 5)** compared to cytoplasm (pH 7.2). Lysosomal enzymes are **acid hydralases** - i.e., they function best at acidic pH.
- Targeting of **proteins to lysosomes** is **Mannose-6-phosphate** dependant and targets the newly synthesized lysosomal hydrolases to the lumen of the lysosome.
- Types of lysosomes and their functions are mentioned in the flowchart below.
- **Phagolysosome** = autophagic vacuole + primary lysosome.
- **Residual bodies:** After materials in phagosome have been digested, some undigestible remain maybe left in the lysosome - called residual bodies.
- **Acrosome**, in the head of sperm is a specialized lysosome that contains many hydrolytic enzymes - helps in penetration of ovum by sperm.

CYTOSKELETON

	Microfilament	Intermediate filament	Microtubule
Shape	Double stranded helical arrangement	Tubular hollow	Long, non-branching
Diameter	7 nm	10 nm	25 nm
Basic protein unit	Actin	Various proteins	Tubulin
Location in cell	<ul style="list-style-type: none">• Forms network adjacent to cell• Core of <i>microvilli</i>• Contractile elements of muscle	<ul style="list-style-type: none">• Extend across cytoplasm connecting desmosome and hemidesmosome• The nuclear lamina• In skin epithelium as keratin	<ul style="list-style-type: none">• Mitotic <i>spindle</i>• Core of <i>cilia, flagella</i>
Major functions	<ul style="list-style-type: none">• Essential element of contractile unit of muscles	<ul style="list-style-type: none">• Provide mechanical strength and link cells together	<ul style="list-style-type: none">• Movement of cilia• Provides network for movement of organelle

Flowchart 3.1: Types of lysosomes and their functions



PEROXISOME

- These organelle have a diameter of 0.5 microns only and hence called *microbodies*.
- They are formed by budding or division of *SER*.
- They contain *oxidases* (for *beta oxidation* of long chain fatty acids) and *catalases* (protect cells from oxidative stress).

Diseases of abnormal/absent peroxisomes are:

- Zellweger syndrome
- Infantile Refsum disease
- Adrenoleukodystrophy
- Primary hyperoxaluria.

CENTROSOMES

- Centrosome is located *close to nucleus* and is formed by **two centrioles** placed at right angles to each other.
- The subunits of microtubules in centrosomes are **gamma-tubulins**.
- Centrosomes are **microtubule-organising centres** (MTOCs).
- They regulate **chromosome movement** during cell division.

More MCQ Info About Cytoskeleton

- Microtubules are **polar** with assembly (polymerisation) at one end (the **plus end**) and disassembly (depolymerisation) at the other end (**minus end**). The **plus end grows faster** than the minus end.
- Since microtubules undergo rapid assembly and disassembly, they are said to be in a state of **dynamic instability**.
- **GTP** is required for microtubule assembly.
- **Centrosomes** and **basal bodies** are microtubule organising centers.
- **Chedlak-Higashii syndrome** is due to **microtubule polymerization defect** resulting in ↓ phagocytosis.
- **Drugs that act on microtubules:** **Mebendazole/thiabendazole**, **Griseofulvin**, **Colchicines**, **Vincristine/vinblastine**, **Paclitaxel**. [{"*Maybe The Greasy Collar Wins the Pack (of soap)*"}]
- **Microfilaments** are abundant in **lamellipodia**.
- **Proteins of intermediate filaments** are cell specific and hence used as cell markers. Examples are.
 - **Cytokeratin**—epithelial cells
 - **Vimentin**—fibroblasts
 - **Desmin**—muscles
 - **Lamins**—nuclear lamina
 - **GFAP** (Glial fibrillary acid protein)—Glial cells.

Molecular Motors

- **Microtubular based:**
 - **Dynein** (**retrograde transport**),
 - **Kinesin** (**anterograde transport**).
- **Actin based:** **Myosin I-V**.
 - **Myosin II** is involved in **muscle contraction**,
 - **Myosin V** in **transport of vesicles**.

INTERCELLULAR CONNECTIONS

A. Junctions that tie cells together

1. Tight junctions (zonula occludens)

- Commonly found in **epithelium** of the **GI tract**, **nephrons**, **urinary tract**, **hepatobiliary tract** and **choroid plexus**.
- Tight junctions are located towards **apical region** of cells.
- Membrane proteins forming tight junctions are **occludin**, **claudins** and **junctional adhesion molecules (JAMs)**.
- They permit the passage of some ions and solute in between adjacent cells (**paracellular pathway**).

2. Anchoring junctions

a. Cell-to-Cell anchoring junctions

- **Desmosomes:**
 - Characterized by **focal thickening** of two adjacent cell membranes.
 - **Intermediate filaments** are attached to thickened areas
 - Contains **desmoglein**; **Anti Desmoglein-3 (Anti Dsg3)** antibodies are found in **pemphigus vulgaris**.
- **Zonula adherens (intermediate junctions)**
 - Continuous structure on the basal side of tight junctions, and it is a major site for attachment of intracellular **microfilaments**
 - it contains **cadherins**

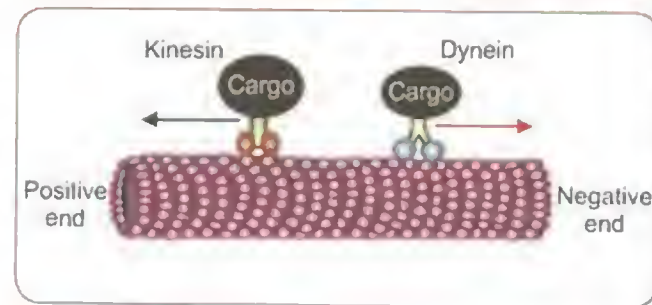


Fig. 3.1: Kinesin and dynein motor molecules

Cilia

- **Motile cell processes**; contain a core of microtubules called **axoneme**; axoneme consists of 9 doublet microtubules uniformly spaced around 2 central microtubules (**9 + 2 arrangement**); **Nexin** connects the 9 doublets.
- Each doublet has short arms that consist of **dynein ATPase** which splits ATP to provide energy for cilia movement.
- **Kartagener's syn.:** **Immotile cilia** due to a **dynein arm defect**. Results in **male and female infertility** (immotile sperms and immotile Fallopian tube), **recurrent sinusitis** and **bronchiectasis a/w situs inversus**.

Rafts and Caveolae

- Some areas of the cell membrane are especially rich in cholesterol and sphingolipids and are called **rafts**.
- The **rafts** are the precursor of flask-shaped membrane depressions called **caveolae** (little caves) when their walls become infiltrated with protein called **caveolin**.

Contd...

Contd

A. Junctions that tie cells together

b. Cell-to-Basal lamina anchoring junctions

- **Hemidesmosome:**
 - They attach cells to underlying basal lamina and extracellular matrix
 - They are connected intracellularly to **intermediate filaments**.
 - They contain **integrins**.
 - Anti-hemidesmosomal antibodies are seen in **Bullous pemphigoid (BPAG1 and BPAG2)**
- **Focal adhesions**
 - Attach cell to basal lamina
 - They are a/w **actin** filaments and assist in **cell movement**.

B. Junctions that allow transfer of Ions and molecules

Gap junctions

- Here the intracellular space **narrows from 25 nm to 3 nm**.
- Made up of **connexons** which is made up of six identical protein subunits called **connexins**.
- Permits substances to pass between cells **without entering ECF**.
- Gap junctions allow ions to pass through easily and serve as **electrical synapses - physiologic syncytium**.
- Sugars, amino acids and solutes with **molecular weight upto 1000** can pass from cell to cell.
- Mutations of connexon genes - **Chorcot Marie Tooth disease**; a/w **peripheral neuropathy**

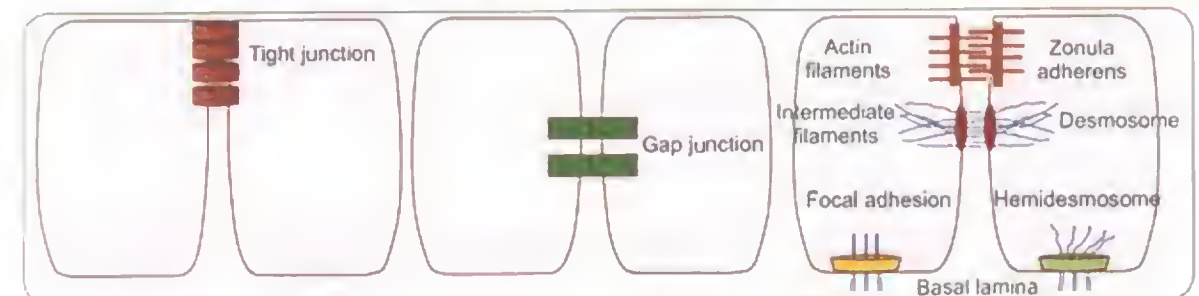


Fig 3.2: Schematic representation and locations of specialized junctions connecting the cells

NERVE PHYSIOLOGY

NEURON

Important numbers about nerves

- Number of neurons: 10^{11} (100 billion)
- Number of glia: 10-50 times more than number of neurons
- Number of synapses made by 1 neuron = 2000
- Number of dendrites per neuron: 10,000.
- Total number of synapses: 2×10^{14}
- About 40% of human genes participate in the development of CNS.

Parts of a Neuron

- **Perikaryon** (also known as **soma** or **cell body**): It contains the **nucleus** and **cytoplasm** containing **cell organelle**

- **Nucleus:** Contains one or two nucleoli but **centrioles are absent**
- **Cell organelle:** Nissl granules, golgi apparatus, mitochondria and lysosomes.
- **Cytoplasm** also contains cytoskeletal proteins like neurofilaments (**neurofibrils**), microtubules and actin filaments.
- **Dendrites:** are known as **receptor zone** where **graded electrogenesis** occurs.
- **Axon hillock:**
 - Thickened area of the cell body from where **axon** arises;
 - It **lacks Nissl granules** (RER), free ribosomes and Golgi apparatus.
 - **Initial segment** (50-100 microns): The first unmyelinated portion of the axon

➤ Axon hillock - initial segment region has the **lowest threshold for excitation** since they have a much higher density (350-500/mm²) of voltage gated sodium channels.

➤ Axon hillock is the **trigger zone/generator area** since it is the site where the **action potentials are generated**.

- **Axon terminal:** Divides into several branches called **telodendria** and their ends form **synaptic knobs**.

EXTRA EDGE

- **Nissl granules** are **RNA rich, basophilic** structure composed for rough endoplasmic reticulum (RER). It is the **biosynthetic apparatus** of the neuron.
- They are **ABSENT** in the axon hillock and axon.
- They are **abundant** in highly active cells such as **spinal motor neurons**.

Myelin

- **Schwann cells** form the myelin sheath around axons in the **peripheral nervous system**.
- In the **CNS, oligodendrocytes** cause myelination.
- The Schwann cell wraps several times (about 100 times) over 1mm length of the axon. Thus the myelin sheath

extending along the length of an axon is formed by many Schwann cells.

- The gap between the Schwann cells are called **nodes of Ranvier** (where the plasma membrane is exposed to ECF).
- **Node of Ranvier** has the **highest concentration of Na⁺ channels** (2000-12000) per square micrometer of cell membrane.
- **Protein zero (P0)** is present in Schwann cell membrane. Mutation of P0 cause **peripheral neuropathies**.
- Timing of myelination during development:
 - **Sensory fibres of dorsal column** first get myelinated, which occurs at 4th-5th month of intrauterine life.
 - **Corticospinal tract** fibres start myelinating at 2 months of age and the process gets **completed by 2nd year of life** when the child has learned to walk.
- Uses of myelination:
 - It **increases speed** of conduction
 - It **reduces energy expenditure** of the cell
 - It provides a **protective covering** to the axon
 - Gives **white color** to the white matter of brain and spinal cord.

Axonal (Axoplasmic) Transport

Transport type	Speed	Remarks
Fast antegrade (plus end directed, i.e., from cell body towards the axon terminal which is the plus end/growing end)	400 mm/day	<ul style="list-style-type: none"> • Occurs with help of kinesin. • Substances transported: many organelle, vesicles and membrane glycoproteins occurs.
Fast retrograde (minus end directed, i.e., from the axon terminal to the cell body- minus end)	200 mm/day	<ul style="list-style-type: none"> • Occurs with help of dynein. • Substances transported: viruses (VZV in herpes zoster); toxins (tetanus toxin); nerve growth factors and reuptake of synaptic transmitters. • Mapped by horseradish peroxidase
Slow antegrade	0.5-10 mm/day	<ul style="list-style-type: none"> • Mechanism not clear; possibly molecular motors. • Substances transported: cytoskeletal elements (microfilament, microtubules, actin)

Types of Neurons

According to Arrangement of Axon

- **Unipolar neuron:** These neurons have only one process; usually found in **invertebrates**; in man they are found in **mesencephalic nucleus of Vth cranial nerve**.
- **Pseudounipolar neurons:** An axon after originating from the soma splits into two, both of which function as axons - one going to skin or muscle and the other to the spinal cord. Example is the **dorsal root ganglion neuron (sensory neuron)**

- **Bipolar neuron:** These neurons have a specialised axon and dendrite; examples are bipolar cells in **retina**; olfactory epithelium; sensory ganglia of cochlea and vestibular nerves.
- **Multipolar neuron:** have one axon and many dendrites; Examples are **spinal motor neurons**; hippocampal pyramidal cells and cerebellar Purkinje cells.

According to Length of Axon

- **Golgi type 1 neuron**

- Have a **long axon** that maybe 1 m in length
- Examples: long fibre tracts of brain (**corticospinal tract**) and spinal cord, peripheral nerves.
- **Golgi type 2 neurons**
 - Have **short axons**.
 - Examples: **inhibitory neurons** of cerebral and cerebellar cortex.

NERVE POTENTIALS

Terms used for Membrane Potentials

- **Polarised:** When there is a voltage difference between the inside and outside of the membrane, the membrane is said to be **polarised**.
- **Depolarised:** When the membrane potential becomes positive or less negative (i.e., closer to zero) its is said to be **depolarised**.
- **Repolarisation:** Return of potential to resting value after depolarisation phase.
- **Hyperpolarised:** When the interior of the cell becomes more negative in relation to RMP, the membrane is said to be **hyperpolarised**.

While stimulating the nerve, the following events occur sequentially:

1. Electrotonic (Graded) Potential

- These are **local, non-propagated** potentials of **small magnitude**, in response to **passive addition of charge**.
- **Catelectrotonic potential:** The cathodal end of stimulus evokes a **depolarising** response.
- **Anoelectrotonic potential:** Anodal end of stimulus evokes a **hyperpolarising** response.

2. Local Response

- When electronic potential reaches upto a certain level, say from -70 mV to -63 mV, gradual opening of voltage gated Na⁺ channels occurs and leads to a localised potential - the local response.
- **Similar to graded potential**, the local response **dies out** with increasing distance.

Causes of Different Phases of Action Potential

Phase of potential	Cause
Electrotonic potential	Passive addition of charge on membrane surface
Local potential	Opening up of few Na ⁺ channels
Depolarisation phase of AP	Na⁺ Influx: Opening up of many voltage gated Na ⁺ channels
Repolarisation phase of AP	K⁺ efflux: Increase in K ⁺ exit from cell and inactivation of Na channels
After hyperpolarisation phase of AP	Slow return of the K ⁺ channels to the closed state

- Local response is seen **only** with **depolarising stimulus** of lower strength and not a hyperpolarising one.

3. Action Potential

- Described in detail below.

ACTION POTENTIAL

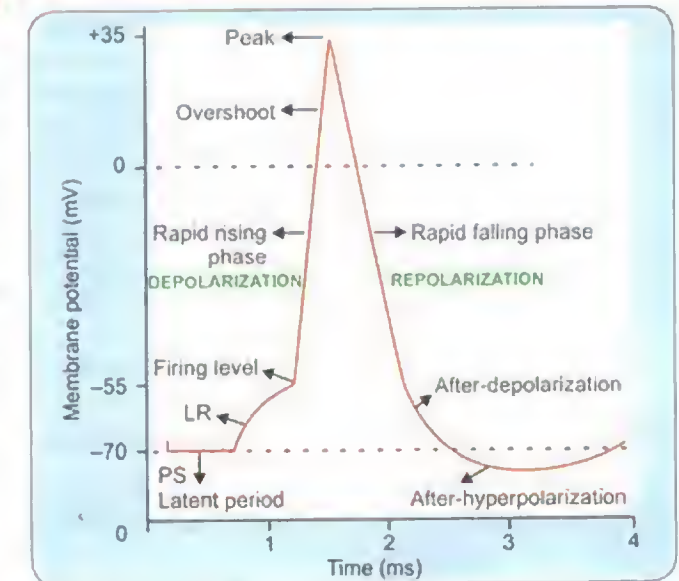


Fig. 3.3: Phases of action potential recorded from a neuron. Note, depolarization phase, overshoot and peak; and repolarization phase consists of rapid falling phase and after-depolarization. (LR: Local response; PS: Point of stimulation)

- **Definition:** Action Potential (AP) is a transient change in membrane potential of **about 100 mV** (-70 to +35 mV), which is conducted along the axon in an **all-or-none** fashion.
- AP is propagated with the **same size (amplitude) and shape** along the entire length of the axon.
- Duration of a single AP = about **1 msec**.
- It is also known as **impulse potential** or **spike potential**.

EXTRA EDGE

- **Hodgkin's cycle:** The opening of few Na^+ channels leading to further opening of other Na^+ channels is called Hodgkin's cycle. This is an example of **positive feedback** control where a stimulus triggering an event further facilitates the process.

Refractory Period

- **Absolute refractory period (ARP)**
 - Period when a cell is unable to fire an AP no matter how strongly it gets stimulated.
 - ARP corresponds to the time from when firing level is reached until repolarisation is $1/3$ complete.
 - The cell is refractory since a large fraction of Na^+ channels are voltage inactivated and cannot be reopened until membrane is repolarised.
- **Relative Refractory Period (RRP)**
 - Starting from the point when repolarisation is $1/3$ complete to the end of after-depolarisation.
 - A stronger than normal stimulus (**suprathreshold**) can open up sufficient number of Na^+ channels to elicit an AP during the RRP.

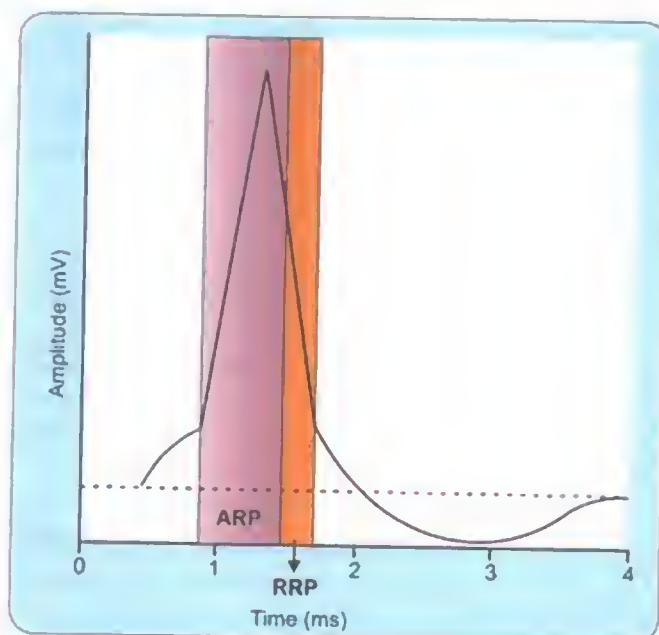


Fig. 3.4: Refractory periods of nerve action potential. (ARP: Absolute refractory period; RRP: Relative refractory period)

Other Types of Action Potential

- **Bi-phasic potential:** This type of AP is obtained when both recording electrodes are on the **surface** of the nerve about **1 cm** apart.

- **Compound action potential (CAP):** When a nerve bundle is stimulated, more than one axon may be excited. The electrical recording of the combination of AP produced is called CAP. Its features are:
 - It is also a bi-phasic AP
 - It does NOT follow all or none law.
 - It is a multi-peaked AP
 - Seen in mixed nerve bundle.

Conduction of Action Potential

- **Myelination:** Increases conduction velocity in axons by the following effects.
 - By increasing axon diameter (conduction velocity is proportionate to the diameter of the fibre; **larger the fibre, greater the velocity** - since large diameter fibres have less cytoplasmic resistance for flow of ions)
 - **Membrane resistance (R_m) is high** in myelinated nerve fibres = faster conduction
 - **Low Membrane capacitance** = faster conduction of AP.
 - By saltatory conduction (see below)
- **Lower temperature slows down** conduction velocity.

Saltatory Conduction

- Depolarization in myelinated axons **jumps from one node of Ranvier to the next**, with current sink at the active node serving to electronically depolarize the node ahead of the action potential to the firing level.
- Myelin is an effective insulator and current flow through it is **negligible**.
- This jumping of depolarization from node to node is called **saltatory conduction**.
- It is a **rapid process** that allows myelinated axons to conduct up to 50 times faster than unmyelinated fibers.

Ortho- and Antidromic

- Experimentally, an axon can conduct in **any direction**.
- But in the human body (natural situation) impulses are conducted in **one direction only** (i.e., from synaptic junction/receptors along axons to their termination. This is **orthodromic** conduction.
- In nerve fibres, conduction is unidirectional because transmission across synapse and neuromuscular junction is unidirectional.
- Conduction in opposite direction is called **antidromic**, BUT antidromic conduction will fail to pass the first synapse they encounter and die out at that point.

Strength Duration Curve

- Quantitatively stimulus has two characteristics: **intensity (strength)** and **duration (time)**.
- In general, **stronger the stimulus, lesser is the duration** required to produce an AP.
- Strength-duration curve gives idea about excitability of a tissue; **chronaxie** is a better indicator than rheobase.
- **Rheobase:** The minimum **current strength** required to elicit action potential in excitable tissue (nerve, muscle) is called the **rheobase**. It is **measured in milliamperes (mA)**. (Remember school physics!—**Rheostat** is for current).
- **Chronaxie:** It is the **duration** of current required to excite the tissue (nerve, muscle) with a current strength of **double the rheobase**. It is **measured in milliseconds**. (Chronology is for time/duration!).
- Lesser the chronaxie (lower threshold), more is the excitability.
- Chronaxie: Nerve \ll skeletal muscle \ll myocardium \ll smooth muscle (means **nerve is most excitable** - Aa nerve is most excitable).

- **Right and upward shift** of the curve occurs when the tissue is **less excitable**.

Differences between Graded (Local) Potential and Action Potential

Local (Graded) potential	Action potential
Proportional to stimulus strength (graded)	Independent of stimulus strength
Does not follow all-or-none law	Follows all-or-none law
Not self propagated but decremental with distance	Propagated unchanged in amplitude
Can be summed	Cannot be summed
Can be a depolarising or hyperpolarising potential	Always a large depolarising potential
Due to opening of ligand-gated or leaky-ion channels	Due to opening up of voltage-gated ion channels
Does not have threshold or refractory period	Has a threshold and refractory period

NERVE FIBRE CLASSIFICATION

Fibre type (Erlanger and Gasser)	Numerical type (Lloyd and Hunt)	Functions	Fibre diameter (microns)	Conduction velocity (m/s)
A alpha	Ia and Ib	Proprioception (golgi tendon organ); somatic motor	12-20 (thickest)	70-120 (maximum)
A beta	II	Touch, pressure	5-12	30-70
A gamma		Efferent to muscle spindles	3-6	15-30
A delta	III	Pain ('first pain' or ' fast pain' or ' epicritic pain' - a well localised sharp prick), temperature (cold)	2-5	12-30
B		Pre-ganglionic (sympathetic main), autonomic	<3	3-15
C (Dorsal root), unmyelinated	IV	Pain ('second pain' or ' pruritic pain'; - poorly localised dull pain), temperature (warm)	0.4-1.2	0.5-2.0 (slowest)
C (sympathetic), unmyelinated		Post-ganglionic autonomic (sympathetic main)	0.3-1.3 (thinnest)	0.7-2.3

Susceptibility of Nerve Fibres

Stimulus	Susceptibility (Most to Least)
Pressure	A > B > C (A-alpha, largest diameter, most susceptible)
Hypoxia	B > A > C
Local anesthesia	Aδ > Aγ > Aβ > Aα > B > C

Note

- Physiology and Anesthesia textbooks vary in this matter — BUT this has been referred from latest anesthesia textbooks which have clarified that type C fibre is most resistant.

SYNAPTIC TRANSMISSION

- Arrival of AP at the axon terminal causes opening of voltage gated calcium channels and causes **calcium influx**.
- Calcium mediated exocytosis of neurotransmitter vesicles is facilitated by membrane proteins **synaptobrevin** and **syntaxin**.
- Binding of ACh to ACh receptor causes **Na⁺ influx** that leads to genesis of a **depolarizing potential** - the **end plate potential** (EPP). (EPP is **always** a depolarising potential!).
- End plate potential is like a **graded potential** and has all the features of a local/graded potential (as described earlier above in table of differences between local potential and action potential).
- **Small quanta (packets) of ACh** are released randomly from the nerve cell membrane at rest. Each produces a miniature **depolarising spike** called a **miniature end plate potential** (MEPP) which is about **0.5 mV** in amplitude.
- **Botulinum toxin** causes **presynaptic blockade**.
- **Curare** causes **postsynaptic blockade**.

Postsynaptic Potentials

- When molecules of neurotransmitters bind to postsynaptic receptors, they may produce two outcomes as below:

EPSP	IPSP
<ul style="list-style-type: none"> • A slight depolarisation of post-synaptic membrane called the excitatory post-synaptic potential. • It occurs due to opening of ligand-gated Na⁺ channels (Na⁺ influx) 	<ul style="list-style-type: none"> • A slight hyperpolarisation of post-synaptic membrane called the inhibitory post-synaptic Potential (IPSP). • It occurs due to opening of ligand-gated K⁺ (K⁺ efflux) and Cl⁻ channels (Cl⁻ influx)

NERVE INJURY

Seddon's Classification of Nerve Injury

Neurapraxia	Axonotmesis	Neurotmesis
<ul style="list-style-type: none"> • Minor contusion of the peripheral nerve caused by lack of blood flow or by pressure on the affected nerve • Axis cylinder is preserved, i.e. no loss of structural continuity. e.g.: Saturday night palsy, Crutch palsy. • Temporary: Recovery is complete in 3–6 weeks. • The rate of recovery of axon is 1 mm/day • NO motor march or Wallerian degeneration 	<ul style="list-style-type: none"> • Endoneurium and Neural tube are intact. • Axons are disrupted. • Spontaneous recovery is expected in few months, e.g.: tardy ulnar nerve palsy • Motor march is seen: Recovery of the motor innervation in a progressive manner from proximal to distal (i.e. the muscle nearest to the site of injury recovers first). • Wallerian degeneration maybe seen 	<ul style="list-style-type: none"> • Complete anatomic cut in the nerve. • Most likely permanent injury without repair, and will likely only achieve partial recovery at best. • The part of the neuron distal to the point of injury undergoes secondary or Wallerian degeneration

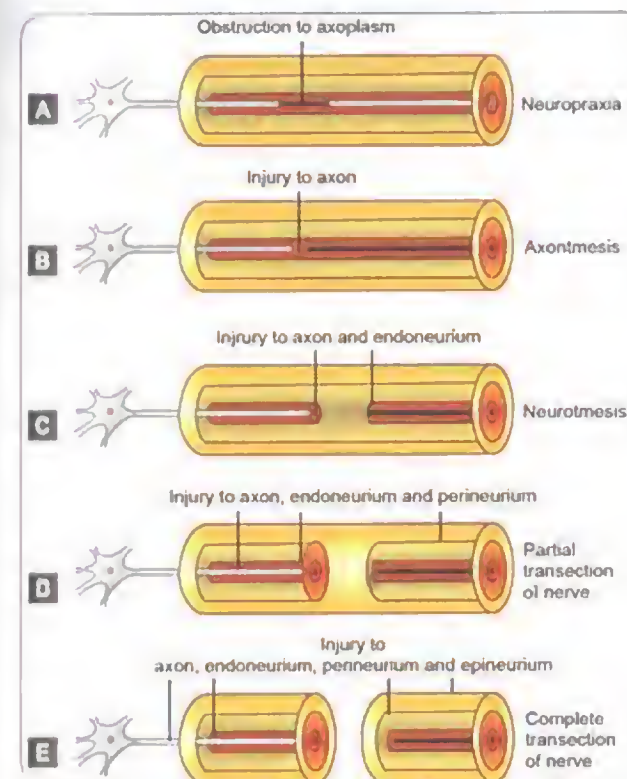
- Both EPSP and IPSP can last for **5-10 milliseconds** (greater than AP which lasts for 1ms).
- Both EPSP and IPSP are local potentials and have all the features of a local/graded potential (as described earlier above in table of differences between local potential and action potential).

Renshaw Cell Inhibition

- **Renshaw cells** are **inhibitory interneurons** found in the **gray matter of the spinal cord**, and are associated in two ways with an **alpha motor neuron**.
- They receive an excitatory collateral from the alpha neuron's axon as they emerge from the motor root, and are thus "kept informed" of how vigorously that neuron is firing.
- Next, they send their own inhibitory axon to synapse with the cell body of the initial alpha neuron.
- A Renshaw cell may be supplied by more than one alpha motor neuron collaterals and it may synapse on multiple motor neurons.
- Renshaw cells thus act as "**limiters**," or "**governors**," on the alpha motor neuron system (by utilize the inhibitory neurotransmitter **glycine**), thus helping to prevent muscular damage from tetanus.
- In this way, Renshaw cell inhibition represents a **negative feedback mechanism**.
- **Strychnine** specifically acts on these cell's ability to control alpha motor neuron firing by binding to the glycine receptors on the motor neuron and thus muscles continually contract and may prove fatal.
- **Cl₂ tetani** (**tetanus toxin**) acts on **synaptobrevin** and prevents its attachment with **syntaxin**—this **prevents release of GABA** from vesicles at different synapses in the CNS and produces spastic paralysis.

Sunderland's Classification

- More **clinically accepted**
- Arranged in ascending order of severity from degrees 1-5 (4,5 have no recovery).
 - Degree 1—corresponds neuropraxia;
 - Degree 2,3,4—correspond to axonotmesis;
 - Degree 5—corresponds to neurotmesis;
 - Degree 6 (of Mackinnon Dellon) - a combination of varying degrees of Sunderland which co-exist in the same nerve.



Figs. 3.5A to E: Sunderland histologic classification of peripheral nerve injury is helpful in understanding the results of electrical tests.

EXTRA EDGE

- **Peripheral nerves** can withstand **ischemia upto 3 hours**.
- **Traction** nerve injury is usually **axonotmesis** and prognosis for regeneration is good.
- In all open wounds with clinical signs of nerve injury, **nerve exploration** should always be done.
- **Tinel's sign** provides evidence of regeneration of nerve (not the accurate location of lesion).
- **Nerve conduction studies** and electromyography (EMG) are performed minimum **3 weeks after injury** for any response to be demonstrable.

Nerve Degeneration

- **Distal to the site of injury** (secondary or "**Wallerian**" degeneration)
 - Following changes are seen in the axon in sequence starting **within 24 hours** after the cut:
 - The axis cylinder (axon with its endoneurium) breaks into small **rodlets** and degenerates completely. **First there is degeneration of axon** followed by myelin.
 - Myelin sheath disintegrates into fat droplets (by 8-35 days).
 - **Neurilemma** remains **intact**.
 - Schwann cells proliferate rapidly.
 - Macrophages remove debris of axis cylinder.
 - Hollow neurilemmal tube is filled with Schwann cell cytoplasm - **Ghost tubes**.
- **Proximal to site of injury** (primary or retrograde degeneration)
 - Degenerative changes are also seen in the proximal fragment (upto the first node of Ranvier) and in cell body of neuron.
 - **Chromatolysis:** Nissl hodies degenerate into granules.
 - **Golgi apparatus disintegrates**.
 - Cell body swelling
 - **Neurofibrils** disappears
 - Nucleus is pushed to periphery.

MUSCLE PHYSIOLOGY

MUSCLES

Skeletal muscle

- Has well developed **cross striations**,
- is under **voluntary control**,
- lacks anatomic and functional connections between individual muscle fibres.

Cardiac muscle

- Gas **cross striations**,
- BUT it is **functionally syncytial** and rhythmically **contracts without external innervations** owing to the presence in the myocardium of **pacemaker cells that discharge spontaneously**

Smooth muscle

- Lack cross striations,
- Found in **most hollow viscera** and in the **eye**.

SKELETAL MUSCLE

Physiologic Anatomy of Muscle Fibre

- Each **muscle fibre** is a single cell that is long, multinucleated, cylindric and surrounded by a **cell membrane**, the **sarcolemma**. The muscle fibre is in turn made up of **myofibrils** in turn made up of individual filaments made up of **contractile proteins**.

Muscle Contractile Proteins

1. Contractile Proteins

- **Actin:**
 - Major protein of the **thin filament**.
 - **F-actin** (filamentous actin) forms the backbone of the thin filament.
 - F-actin is supported by **nebulin**.
- **Myosin:**
 - Thick filaments are polymers of **myosin-II**.
 - Myosin head functions as an **ATPase**.
 - Length 1.6 microns and MW 480,000.

2. Regulatory Proteins

- **Tropomyosin:**
 - It is the other protein of the **thin filament**.
 - Tropomyosin **covers the myosin-binding sites** on the actin monomers.
 - Each **thin filament** contains **300-400 actin** molecules and **40-60 tropomyosin** molecules.
- **Troponin:**
 - Troponin is also a protein of thin filament.
 - It is a Ca^{2+} binding protein that regulates the action of Ca^{2+} on tropomyosin.
 - It is made of 3 protein subunits:
 - Troponin **T**: Binds to Tropomyosin
 - Troponin **I**: Inhibits myosin-actin interaction
 - Troponin **C**: Binds Calcium (has 4 calcium binding sites) and brings about Contraction by removing effect of tropomyosin.

3. Attachment Proteins

- **Titin** (connectin): It is the **largest known protein** (27,000-33,000 amino acids; > 3000 kDa); it **connects Z lines to the M lines** and provides scaffolding to the sarcomere; **elasticity** of muscle is due to this protein.
- **Desmin** binds the Z lines to the sarcolemma (plasma membrane).

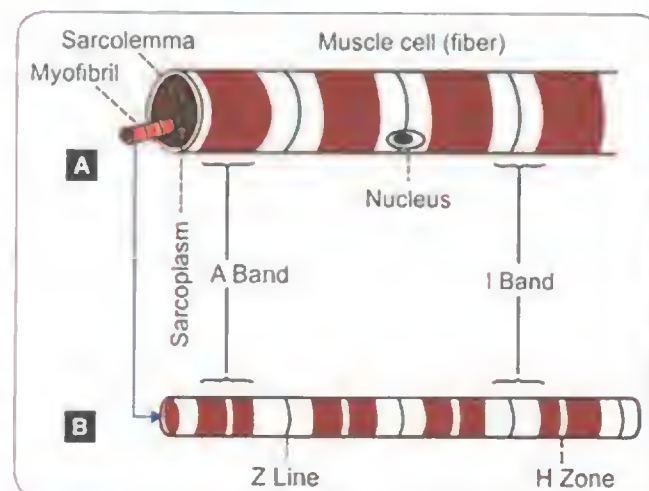
- **Nebulin**: Stabilises length of actin filaments during contraction
- **Myomesin**: Binds titin with M line.
- **Dystrophin**:
 - Dystrophin anchors the thin filaments to the membrane spanning protein **beta- dystroglycan** (a glycoprotein) - dystrophin-dystroglycan complex.
 - This complex adds strength to the muscle sarcolemma by providing **scaffolding to the fibrils** and connecting them to the extracellular environment.

More Dystrophin Points

- The **DMD gene** is the **largest human gene isolated** and is translated into a protein named **dystrophin**.
- **Absent dystrophin** results in **Duchenne's Muscular Dystrophy** ("Doesn't Make Dystrophin").
- **Decreased/alterd dystrophin** results in **Becker's Muscular Dystrophy**. ("Badly Made Dystrophin").
- Dystrophin is **present in skeletal muscle, smooth muscle, cardiac muscle, brain and retina**.
- **Gower's sign**: Child uses his arms to climb up his own legs to get up from the floor - seen in **DMD** patients.
- **Serum Creatine Kinase** is highly elevated in DMD.

Sarcomere

- Differences in the refractive indexes of the various parts of the skeletal muscle are responsible for the cross striations seen.
- The lighter **I band** is divided by the dark **Z line** and the darker **A band** is divided by the lighter **H line**. ("**HAZI** = **H** line is in **A** band and **Z** line is in **I** band").
- The area between two adjacent Z lines is a **sarcomere**.
- Average length of a sarcomere is **2 microns**.



Figs. 3.6A and B: A. One muscle cell; B. One myofibril

Sarcolemma

- Sarcolemma is the **cell membrane** of the muscle fibre; as with other cell membranes - its is also a **lipid bilayer** containing:
 - Lipids: Phospholipids, cholesterol
 - Proteins:
 - **Integral (transmembrane) proteins**: **Dystroglycans, sarcoglycans**, Integrins, Caveolin
 - **Peripheral (surface) proteins**: **Dystrophin**, Dysferlin, Calpain
 - Sugar: As glycolipids and glycoproteins.

Sarcotubular System

- The **sarcoplasm** (cytoplasm) of skeletal muscle contains **sarcotubular system** that consists of **T-tubules** and **sarcoplasmic reticulum (L-tubules)**.
- **T-tubules** (Transverse tubules)
 - These are **infoldings** of cell membrane (sarcolemma) into the muscle cell.
 - L-tubules allow **penetration of the electrical membrane discharge** to the **inner core** of the muscle cell.
 - A thin gap (15 nm) separates the T tubules from the sarcoplasmic reticulum.
 - L tubule has **dihydropyridine receptor (DHPR)** - a **voltage gated L type calcium channel**.
- **L tubules** (longitudinal tubules):
 - This is the **sarcoplasmic reticulum** (smooth endoplasmic reticulum). It extends between two L-tubules in a longitudinal fashion.
 - Dilated portions at both ends of the sarcoplasmic reticulum nearest the T tubules are called **terminal cisterns**-storehouse of calcium ions and site of calcium release.
 - **Calsequestrin** is a calcium binding protein within terminal cisternae.
 - The two cisterns (on either side of the T tubule) and the T tubule are together called a **triad**; in cardiac muscle it is a **diad**.
 - The L tubule cistern has **ryanodine receptor (RyR)** - a **ligand gated calcium channel**.
- **SERCA** = Sarcoplasmic Endoplasmic Reticulum Calcium ATPase - it is a **Ca-Mg-ATPase** that pumps out free calcium ions from sarcoplasm (cytoplasm) into the cisterns of sarcoplasmic reticulum (this decrease in sarcoplasmic Ca^{2+} concentration causes muscle relaxation)

EXTRA EDGE

- **Malignant hyperthermia**: Mutation of the **ryanodine (RyR)** channel results in an inefficient feedback mechanism to shut down calcium release after stimulation of the RyR - thus causes **increased muscle contraction and heat generation** (Topic discussed in detail in Anesthesia Chapter (Pg 1147)).

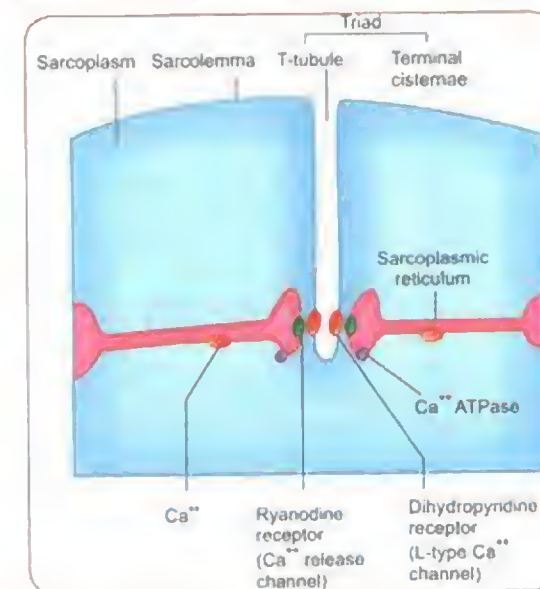
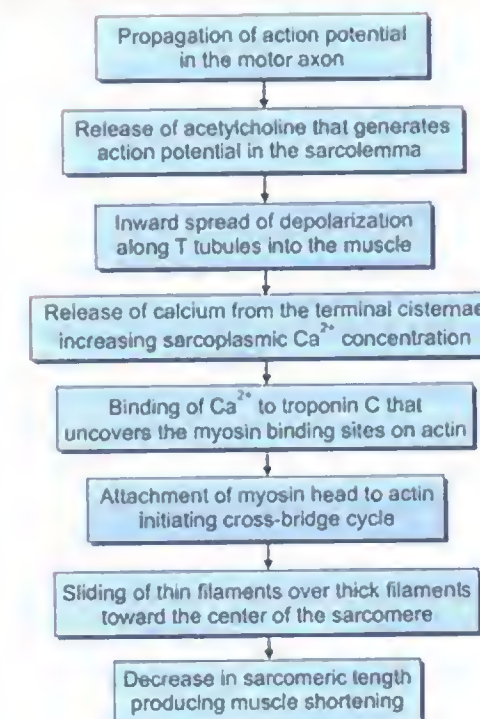


Fig. 3.7: Structure of sarcotubular system

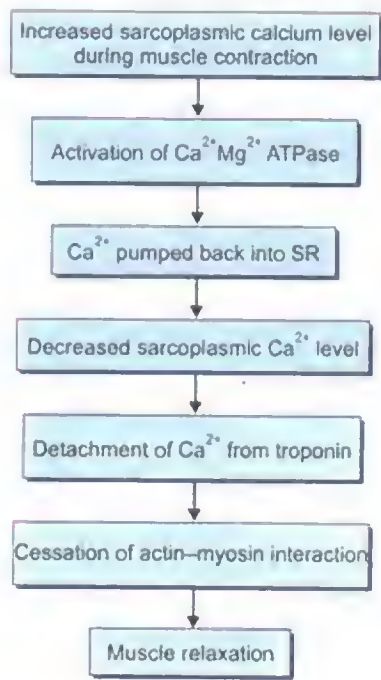
Excitation Contraction Coupling

- The process by which depolarisation of a muscle fibre initiates contraction is called **excitation contraction coupling**.
- The events during excitation and contraction are summarised in the below flowcharts 3.2 and 3.3.

Flowchart 3.2: Major steps in molecular mechanism of skeletal muscle contraction.



Flowchart 3.3: Major events in skeletal muscle relaxation.



Sliding Filament Theory

- **AF Huxley** proposed the *sliding filament theory* of muscle contraction.
- Shortening of muscle fibres occurs due to *sliding of thin filaments over thick filaments* toward the centre of the sarcomere.
- During muscle contraction:
 - Width of **A band** is **always constant** (does NOT change).
 - Width of **I band** **decreases**.
 - Width of **H band** **decreases** (disappears).

Cross Bridge Cycle

- The sequence of events that occur during the interaction between the **myosin cross bridges** and the **actin molecules** is termed **cross-bridge cycle**.
- **Power stroke**: Dissociation of Pi (inorganic phosphate), from the myosin head triggers the **power stroke**, a conformational change during which the myosin head bends on the hinge at an angle of **45 degrees** pulling the actin filament **1 µm** toward the centre of the sarcomere.

Role of ATP in muscle contraction

- ATP **provides energy** for power stroke of the myosin head
- It brings about a **dissociation of the myosin head** from the actin filament
- It brings about **muscle relaxation** by **pumping out** Ca⁺⁺ from the sarcoplasmic reticulum into the terminal cisterns of sarcoplasmic reticulum (through SERCA).

EXTRA EDGE

- If cellular **ATP stores are depleted** as happens **after death**; the cross bridges **cannot detach** and it is called **rigor** cross bridge - the cycle stops there and the filaments remain in the attached state - responsible for **rigor mortis**.

Types of Contractions

	Isometric	Isotonic
Length of muscle	Remains same	Shortening occurs
Tension	Tension increases	No change
External Work	No work done	Work is done
Example	A man pushing against an immovable object such as the great wall of China	A man lifting a cup of coffee to his mouth

EXTRA EDGE

- **Muscle strength** is best improved by **isotonic exercise** (since external work is performed)—example is exercising in the gym.

MOTOR UNIT

- Each single spinal motor neuron along with the muscle fibres it innervates is called a **motor unit**.
- The motor unit is the **functional contractile unit** because all of the muscle cells within a motor unit contract synchronously when the motor nerve fires.
- The number of muscle fibres supplied by a single neuron is known as **innervation ratio**. This ratio is lower in muscle with precise/skilled movements - like **hand and extraocular** muscles - here the ratio is **3-6** (i.e., only 3-6 muscle fibres in a motor unit!). But muscles of back and leg (gross movements) contains 600-1000 fibres per motor unit.
- Motor unit **obeys all or none law**.

Size Principle

- All muscle fibres in a motor unit are of the **same type** i.e. **oxidative** or **glycolytic** in nature.
- Usually the **large diameter, fast-conducting** motor neurons innervate the muscle fibres of the **fast (glycolytic)** motor units and the **small diameter, slow-conducting** motor neurons innervate the muscle fibres of **slow (oxidative)** motor units
- Small diameter motor units innervate slow twitch muscle (oxidative) fibres; large motor units innervate fast twitch muscle fibres.

Henneman Principle

- As strength of muscle contraction gradually increases, **small/slow motor units are recruited first**; then if required the **larger units** are also recruited (for **increasing the strength of contraction**).
- Derecruitment is in opposite order.
- Thus during less intense activity, oxidative fibres take part and in more intense activity glycolytic fibres take part.

Temporal Summation

- **Summation** means adding together of individual twitch contraction to increase the intensity of overall muscle contraction.
- In temporal (frequency) summation, a single motor unit is stimulated by increasing the frequency of contraction.
- **Tetanus**:
 - With repeated stimulation, the individual responses fuse into a **single continuous contraction** - **tetanic contraction** (tetanus).
 - Tetanus is reached when **sarcoplasmic Ca⁺⁺ levels reach their maximum**.
 - **Post-tetanic potentiation**: When a single stimulus is applied to a muscle immediately after the tetanic contraction is over, the amplitude of contraction is higher than that of a single twitch. This is due to **increased intracellular Ca⁺⁺ concentration**.
 - Tetanising frequency (critical frequency) = **1 / twitch duration** (in sec).
 - Tetanic tension = **4 × twitch tension**.
- **Treppe or staircase phenomenon**:
 - When a series of maximal stimuli is delivered to a skeletal muscle at sub-tetanising frequency, tension rises during each twitch. After several contractions, a uniform tension per contraction is reached - known as **treppe**.

TYPES OF MUSCLE FIBRES

	Type I fibers (Red)	Type IIB fibers (White)
Also known as	Slow-twitch fibers, Oxidative fibres, Tonic fibres, S fibres	Fast-twitch fibers, Fast glycolytic fibres, Phasic fibres, F fibres
Myoglobin content	More (hence red color!)	Less (hence white color)
Myosin ATPase activity	Slow	Fast
Metabolism	Aerobic	Anaerobic
Fibre length	Small	Long

Contd...

	Type I fibers (Red)	Type IIB fibers (White)
Fibre diameter	Small	Large
Size of motor neuron	Small	large
Glycolytic capacity	Low	High
Oxidative capacity	High	Low
Capillary density/blood supply	High	Low
Mitochondria	High	Low
Sarcoplasmic reticulum	Moderate	Extensive
Fatigability	Fatigue Late	Fatigue earliest
Action	Muscles that can react more slowly and for longer duration (e.g. antigravity muscles – posture maintaining back muscles, gluteus muscles, leg muscles)	Muscles that act quickly and precisely (e.g. fine skilled movement as in extraocular muscles and hand muscles)

Denervation Hypersensitivity

- Destruction of nerve supply to skeletal muscle can cause abnormal excitability of muscle and increase in sensitivity to circulating ACh.
- **Fibrillation**: Fine irregular contraction of the individual muscle fiber not visible grossly.
- **Fasciculations**: Involuntary contraction of a **single motor unit**; visible grossly.

SMOOTH MUSCLES

Physiologic Anatomy of Smooth Muscle

- Smooth muscle can remain **contracted for longer period** without expenditure of energy.
- Each smooth muscle cell has a **single central nucleus**.
- It has actin and myosin II filaments in the ratio of **10:1** (compared to 2:1 in skeletal muscle).
- **No cross striations** - hence "smooth" muscle.
- Length-tension relationship is **NOT** linear as in skeletal or cardiac muscle.
- **No troponin** (but calmodulin present) and **NO nebulin**.
- **No Z lines** (instead anchorage for actin filaments is provided by **dense bodies**).
- **No T-tubules** but **caveolae** are present.
- Junctions between membrane **gap junctions** and **desmosomes**.

Contd...

Nerve Supply

- **Involuntary** muscle supplied by branches of **autonomic nervous system**.
- Less complex neuromuscular junction present.
- The efferent nerve shows **varicosities** and establishes functional contact at several points on the muscle as it courses alongside - synapse en passant.
- There can be excitatory or inhibitory junctional potentials.

Types of Smooth Muscles

Single-unit smooth muscle

- Muscle fibres are connected to each other by **gap junctions** which enables all the muscle fibres to behave as a single unit- **syncytium** (synchronous electrical and mechanical activity).
- Single-unit smooth muscle is MOST abundant in walls of **hollow viscera**- hence called **visceral smooth muscle** (from esophagus to rectum, gallbladder, ducts of digestive glands, ureter and urinary bladder, uterus and small diameter blood vessels).

Multi-unit smooth muscle

- These do NOT have gap junctions and do NOT behave as a syncytium.
- They resemble skeletal muscles functionally.
- Present in muscles of the **eye (ciliary body and iris)**, **trachea**, precapillary sphincters and **pilaelevator** muscles.

Characteristic Electrical Activities of Smooth Muscle

- There is **NO fixed RMP** (resting membrane potential); average is **-50 mV** (-30 to -70 mV).
- Shape of **action potentials vary widely** which maybe a **sharp spike**, or an AP with **prolonged plateau** or **multiple spikes**.
- **Pacemaker potentials** are recorded in visceral smooth muscles - it **shifts from place to place** and is NOT in a fixed place (as in cardiac muscle).

Mechanism of Smooth Muscle Contraction

- Excitation contraction coupling in smooth muscles is a **very slow** process.
- Calcium enters **into the cell from ECF** (through voltage gated and ligand gated calcium channels).
- This calcium binds to calmodulin.
- **Ca²⁺-calmodulin** complex activates **myosin light chain kinase (MLCK)**, a **phosphorylase**.
- Activation of MLCK causes phosphorylation of myosin- increased myosin ATPase activity - myosin binds with actin causing cross bridge cycling and contraction.
- Relaxation is by dephosphorylation of myosin by myosin light chain **phosphatase (MLCP)**.

- Contraction of smooth muscle via ligand gated Ca²⁺ channels without the generation of an action potential is called **pharmacomechanical coupling**.

Henneman Principle

- Extracellular calcium
- Voltage and ligand gated Ca²⁺ channels.
- Stretch activated Ca²⁺ channels
- Leaky channels
- **Intracellular Ca²⁺** (from sarcoplasmic reticulum)
- Efflux via IP3 (inositol 1-4-5, triphosphate)
- Efflux via RyR channel
- Ca²⁺ stimulated calcium release (**CICR**).

Some UNIQUE Features of Smooth Muscle Contraction

- **Slow** cycling of cross bridges: hence contraction is **slow and sustained**.
- **Low-energy** is required to sustain smooth muscle contraction.
- **Maximum tension** (force of contraction) generated by smooth muscle (4-6 kg/cm²) is **greater than** for skeletal muscle (3-4 kg/cm²)
- **Latch mechanism**:
 - This is a state in smooth muscles, where, even after dephosphorylation of myosin, the cross-bridges continue to 'cling-on' for some time.
 - Thus, it helps to maintain prolonged tonic contraction in smooth muscle for hours with little of energy expenditure (ATP).
 - Latch mechanism occurs when cross-bridge cycling rate is low or zero.
- **Plasticity**: A smooth muscle can readjust its resting length; the length tension relationship for skeletal muscles is NOT valid in smooth muscles.
- **Stress relaxation**: when smooth muscle is stretched, it is unlatched and it relaxes.
- There is a **higher** percentage (80%) of **shortening in smooth muscle** as compared with 30% shortening in skeletal muscle - this is due to polar nature of cross bridges.
- Stretch of visceral smooth muscle leads to development of **spike potentials**, even in the absence of nervous innervation.
- Smooth muscle is **stimulated when stretched**.
- In **pregnancy**, smooth muscle may undergo **hypertrophy** (increase in cell size) and **hyperplasia** (increase in cell number) of myometrium.
- In **hypertension**, when BP is chronically increased, the pressure load acts as a stimulus and the walls of blood vessels undergo **hypertrophy and hyperplasia**.

CARDIAC PHYSIOLOGY

CONDUCTING SYSTEM OF THE HEART

- Anatomy of the heart and conducting system including blood supply have been covered in Anatomy Chapter (Pg 64). The important physiology MCQ aspects will be dealt with here.
- The conducting system is made of modified cardiac muscle.
- The **SA node** (containing **P cells**, small round **Pacemaker cells**) is the **primary pacemaker** of the heart because its **prepotential is steepest** (maximum heart rate).
- **AV node** is called '**gatekeeper**' of the heart since it regulates impulses coming from the SA node.

Conduction Speed of Impulse (Velocity of Conduction)

Tissue	Speed (m/s)
SA node	0.05
Atrial pathways	1
AV node	0.02-0.05 (minimum)
Bundle of His	1

Tissue	Speed (m/s)
Purkinje system	4 (maximum)
Ventricular muscle	1

EXTRA EDGE

- **AV nodal delay**: because conduction in the AV node is slow, a delay of about 0.1 s occurs before excitation spreads to the ventricles. Causes of AV nodal delay are:
 - Small fiber diameter of AV nodal fibers
 - Lesser number of gap junctions
 - Slow type of action potential

Spread/Conduction of Cardiac Impulse

- SA node > internodal pathways > AV node > bundle of His > Purkinje system > all parts of ventricles.
- In the ventricles, **endocardial surface** depolarises **before** epicardial surface.
- **First part of ventricle** to get depolarised is the **endocardial surface at the left side of interventricular septum**.
- **Last part of ventricle** to get depolarised is uppermost part of interventricular septum and posterobasal epicardial surface of left ventricle.

CARDIAC ACTION POTENTIAL

	Fast response AP	Slow response AP
Occurs in	Atrial and ventricular muscles (myocytes) Purkinje fibres	SA node AV node AV junctional tissue Ischemic and injured myocardium
Number of phases	5 phases (0,1,2,3,4)	3 phases (0,3,4); phase 1 and 2 are absent
Phases	<ul style="list-style-type: none"> • Phase 0 (depolarisation); due to influx of Na⁺ • Phase 1 (initial repolarisation); due to closure of Na⁺ channel and efflux of K⁺. • Phase 2 (Plateau) phase); due to Ca²⁺ influx due to prolonged opening of L-type voltage gated Calcium channels • Phase 3 (Final repolarisation); due to increased K⁺ efflux and cessation of Ca²⁺ influx • Phase 4 (Restoration of RMP); restoration of ionic concentrations of Na⁺; K⁺ and Ca²⁺. 	<ul style="list-style-type: none"> • Phase 0 (depolarisation); due to influx of Ca²⁺ • Phase 3 (repolarisation); due to increased K⁺ efflux • Phase 4 (slow diastolic depolarisation); a.k.a prepotential or pacemaker potential (see below)
RMP	Cardiac Myocytes = -90 mV Purkinje fibre = -80 mV	SA node = -50 mV AV node = -60 mV
Max amplitude of phase 0	+ 35 mV	~ + 10 mV

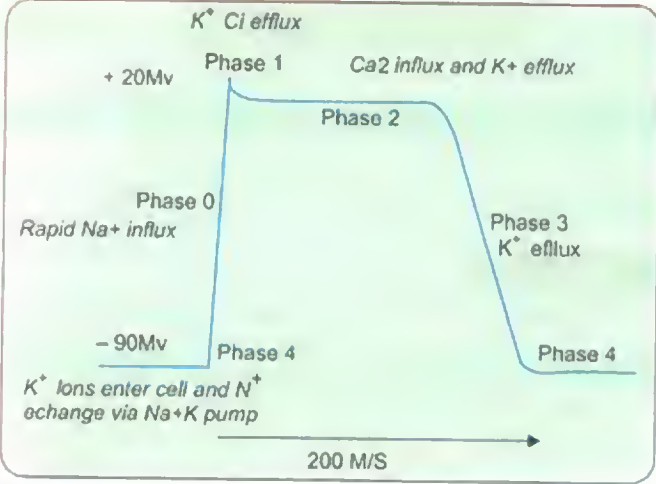


Fig. 3.8: Cardiac action potential

Pacemaker Potential

- Also known as **prepotential** since it brings the membrane potential to the threshold level, which then triggers the action potential. Its ionic basis is given below:
- In early part:
 - Opening of “funny” channels (**HCN channels** - see ‘extra edge’ below) which produce inward **funny current** (“**I_f**”); these are called funny channels since unlike other channels, these are **activated by hyperpolarisation** and they can **pass both Na⁺ and K⁺**.
 - Decreased outward K⁺ current (potassium decay) - thus decrease in K⁺ efflux makes an indirect contribution to pacemaker potential
- In later part: **Inward calcium** current due to opening of **T-type (transient) Ca⁺⁺ channels**.
- **Calcium sparks** (release of calcium locally from sarcoplasmic reticulum) also contribute to pacemaker potential.

EXTRA EDGE

- **HCN channel**= Hyperpolarisation activated Cyclic Nucleotide gated (HCN) channels are intermembrane proteins that serve as nonselective ligand gated cation channels in plasma membrane of heart and brain cells.
- **HCN4** is the main isoform in the **SA node**; it plays major role in generation and modulation of cardiac **rhythmicity**.

Heart-Nerve Supply

- **Parasympathetic** (endocardial location): **Cardio-inhibitory**
 - **Right vagus** → SA node and atria;
 - **Left vagus** → AV node and conducting tissue.

- **Sympathetic** (epicardial location): **Cardiostimulatory** (excitatory)
 - SA node-Right stellate ganglion
 - AV node-Left stellate ganglion
- This has **already** been covered in anatomy, but we repeat this here to understand the below discussion:

Effect of Autonomic Nerves of Heart

Parasympathetic (vagal) stimulation	Sympathetic stimulation
<ul style="list-style-type: none">• Decreased HR (negative chronotropic effect) - right vagus inhibits SA node and causes decrease in slope (flattening) or the pacemaker potential.• Decreased conduction (negative dromotropic) - left vagus inhibits AV node• Increased refractory period of all cardiac cells	<ul style="list-style-type: none">• Increased HR (positive chronotropic)• Increased force of contraction (positive inotropic)• Increased conduction velocity (positive dromotropic)• Increased excitability (positive bathmotropic)• Increased rate of relaxation (positive lusitropic)• Decreased refractory period of all type of cardiac cells

CARDIAC CYCLE

- In cardiac cycle, **mechanical events follow electrical events**.
- Atrial systole starts after ‘P’ wave and ventricular systole starts near the end of ‘R’ wave and ends just after the ‘T’ wave.

Duration of Cardiac Cycle

	Systole	Diastole
Ventricular	0.3 s	0.5 s
Atrial	0.1 s	0.7 s

- Duration of the cardiac cycle = **0.8 s** when HR is **75/min**.
- When HR increases to **200/min** ; duration of cardiac cycle = **0.3 s**.
- When HR decreases to **40/min**; duration of cardiac cycle = **1.5 s**.
- In both the above situations, the **change in length of cardiac cycle** is mainly due to **change in duration of diastole**.
- Thus, in **tachycardia**, **ventricular filling is greatly compromised** due to decreased duration of diastole.

Phases in Cardiac Cycle

Ventricular Systole	
1. Isovolumetric contraction	<ul style="list-style-type: none">• This phase starts with closure of mitral (AV) valve and ends with opening of aortic (semilunar) valve.• Because both valves are closed, there is NO change in volume; hence it is isovolumetric (isometric) contraction• Ventricular wall motion is maximum in this phase.• it is the phase of highest oxygen consumption.
2. Rapid ventricular ejection	<ul style="list-style-type: none">• As the ventricular pressure becomes more than aortic/pulmonary pressure, the semilunar valves open up; blood is suddenly ejected with high velocity.
3. Slow ventricular ejection	<ul style="list-style-type: none">• Ejection velocity reduces in this phase due to decrease in ventricular pressure.

Ventricular Diastole	
1. Protodiastole	Period just before closure of semilunar valves, when blood is moving out of the ventricles due to momentum of blood (even though ventricular muscle has started relaxing).
2. Isovolumetric relaxation	Starts with closure of semilunar (aortic) valve and ends with opening of AV (mitral) valves. Ventricle relaxes as a closed cavity (since all valves are closed) - hence “isovolumic”. Ventricular pressure becomes lowest at this phase.
3. First Rapid filling	Opening of AV (mitral) valves leads to rapid entry of blood into the ventricles - rapid increase in ventricular volume
4. Slow filling (diastasis)	Due to reduced pressure gradient between atria and ventricles, filling occurs slowly in this phase. Ventricular wall motion is least in this phase.
5. Last rapid filling phase	Because of atrial contraction (atrial systole , 0.1s) filling becomes rapid.

EXTRA EDGE

- **Active filling of ventricle** is **30%** (filling due to atrial contraction)
- **Passive filling** of ventricle is **70%** (filling without contraction of atrium).

Cardiac Indices

- The duration of **isovolumetric ventricular contraction** is of considerable clinical importance. Since, it cannot be measured directly, some indices have been devised as approximate measures. These indices can be calculated by
 - Simultaneous **ECG** recording;
 - **Phonocardiogram** (recording of heart sounds) and
 - **Carotid pulse** (indicates aortic pressure change).

- The indices are:
 1. **Electromechanical systole (QS2)**: Time interval between **start of QRS complex** (ventricular activation) to the **second heart sound, S2** (closure of aortic valve). To record this **both ECG and phonocardiography** are required (not carotid pulse).
 2. **Left ventricular ejection time (LVET)**: Time interval between beginning of carotid pressure rise to the diastolic notch (incisura). To record this **ONLY carotid pulse transducer** is required.
 3. **Pre-ejection period (PEP)**: the difference between QS2 and LVET. It gives the duration of electro-mechanical events preceding systolic ejection. To record this, all three - i.e., **ECG, phonocardiogram** and **carotid pulse** are required.
- Normal **PEP/LVET ratio** is **0.35**.

Parameter	Important Notes
Cardiac Output (CO)	<ul style="list-style-type: none">• CO = Stroke Volume X Heart Rate (SV X HR).• In adults, normal SV = 70 mL and HR = 70/min• Thus normal adult CO = 70 x 70 = 4900 ml ~ 5 L/min.
End Diastolic Volume (EDV)	<ul style="list-style-type: none">• Amount of blood in ventricle at end of diastole• Normal EDV = 120 mL
End Systolic Volume (ESV)	<ul style="list-style-type: none">• Volume of blood in ventricle at end of systole• Normal ESV = 50 mL

Contd..

Contd...

Parameter	Important Notes
Stroke volume (SV)	<ul style="list-style-type: none"> Amount of blood ejected by each ventricle/stroke. Normal SV = EDV - ESV (120-50) = 70 ml Also, SV = CO/HR (Cardiac Output/ Heart rate) = 4900/70 = 70 mL.
Ejection fraction (EF)	<ul style="list-style-type: none"> Percentage of EDV that is ejected by each stroke (out of 120 ml, normally 70 mL is ejected; thus EF = ~65%) EF = SV/EDV X 100
Cardiac Index	Cardiac Index = Cardiac output/Body surface area (sq.m) Average cardiac index = 3.2 L/min/sq.m

CARDIAC OUTPUT

Measurement of Cardiac Output

- Fick method:** *Most accurate* method BUT invasive.
- Indicator dye technique** and **Thermodilution technique:** Both based on **Stewart Hamilton principle**.
- Doppler** echocardiographic technique
- Radionuclide imaging technique
- Ballistocardiography**
- Velocity Encoded phase contrast **MRI**

Cardiac Reserve

- The *maximum percentage* that cardiac output can *increase above normal* is called cardiac reserve.
- In a *healthy adult* the cardiac reserve is **300-400%**.

Factors Affecting Cardiac Output

- Since CO is a product of **SV and HR**; it can be regulated by both SV and HR.
- SV affected by **preload, contractility, afterload** and - given in tables below.
- Also, SV increases when *preload increases, afterload decreases or contractility increases*.

Contractility

- Heterometric** regulation of C.O: The factors that change the initial length of myocardium are heterometric regulator - example - *Preload and afterload*.
- Homocentric** regulation of C.O: the factors which change the SV for the same initial length of myocardium. All factors that change contractility (described below) are homocentric regulators.

Contractility (and SV, CO) ↑ with	Contractility (and SV, CO) ↓ with
<ul style="list-style-type: none"> Catecholamine release Digitalis Stressful events (anxiety, exercise) ↑ intracellular calcium ↓ intravascular sodium 	<ul style="list-style-type: none"> β-blocker usage Heart failure Acidosis Hypoxia/hypercapnia Non-dihydropyridine Ca²⁺ channel blockers

Preload and Afterload

Preload	Afterload
<ul style="list-style-type: none"> Preload = ventricular end diastolic volume (the amount of stretching force on cardiac muscle fibres at the end of diastole). Preload pumps up the heart. Preload ↑ with exercise (slightly), ↑ blood volume (overtransfusion) and excitement (sympathetics). Venodilators (e.g. nitroglycerine) ↓ preload. 	<ul style="list-style-type: none"> Afterload = the vascular resistance that ventricles must overcome to produce outflow. Vasodilators (e.g. hydralazine) ↓ afterload. Best index of afterload is Mean Arterial Pressure

Frank Starling Law

- Increasing the end-diastolic ventricular volume causes an increased stretch on cardiac muscle fibers; this leads to an increase in the force of contraction, i.e. Force of contraction is proportional to the initial length of cardiac muscle fiber (preload)

Factors Affecting Heart Rate

No change	Sleep Moderate changes in environmental temperature
Increase	Anxiety and excitement (50-100%) Eating (30%) Exercise (up to 700%) High environmental temperature Pregnancy Epinephrine
Decrease	Sitting or standing from lying position (20-30%) Rapid arrhythmias Heart disease

BLOOD PRESSURE (BP)

- BP is the **lateral pressure** exerted by the column of blood on the walls of the arteries.
- MC used unit of BP is **mm Hg**. BP if expressed in SI units is Kilopascals (kPa).
- Kilopascals may be converted into mm Hg by multiplying by 7.5. Thus BP in mm Hg = (BP in kPa X 7.5) OR **1 mm Hg = 0.133 kPa**.
- Systolic BP (SBP) = 100-119 mm Hg.
- Diastolic BP (DBP) = 60-79 mm Hg.
- Pulse pressure** = systolic BP - diastolic BP. Ratio of stroke volume output to compliance of arterial tree approximately determines **pulse pressure**. Normal pulse pressure = **40 mm Hg** (120-80).
- Mean arterial pressure (MAP)** = diastolic BP + 1/3 pulse pressure. For a BP of 120/80 - the MAP will be **93 mm Hg** (80 + 1/3 of 40 = 80 + 13 = 93)

Blood Pressure Formulae

$$\begin{aligned}
 \text{Mean BP} &= \text{DBP} + 1/3 \text{ PP} \\
 &= \text{DBP} + 1/3 (\text{SBP} - \text{DBP}) \\
 &= (3\text{DBP} + \text{SBP} - \text{DBP})/3 \\
 &= 2/3 \text{ DBP} + 1/3 \text{ SBP} \\
 &= (2 \text{ DBP} + \text{SBP})/3
 \end{aligned}$$

Measurement of BP

- Direct method:** Intra-arterial **manometry**.
- Indirect method:** Sphygmomanometry
- BP cuff is also called **Rivarucci cuff**.
- the **length and width** of the cuff should be **80% and 40%** of the arm circumference (length to width ratio of 2:1).
- Korotkoff's sounds** are due to **turbulent blood flow**.
- Korotkoff's sounds occur in **5 phases**. **Onset of phase 1** corresponds to **systolic pressure**; **disappearance of phase 5** corresponds to **diastolic pressure**.
- Intra-arterial pressure is **always higher** than Sphygmomanometer pressure
- Auscultatory gap:**
 - In older patients with wide pulse pressure and in some hypertensive patients, the Korotkoff's sounds may become inaudible between systolic and diastolic pressure, and reappear as the cuff deflation is continued.
 - This auscultatory gap can be eliminated by **elevating the arm overhead for 30 seconds** before inflating the cuff and bringing the arm to the usual position to continue the measurement.
 - This gap may give **falsely low recording** of systolic BP.

Falsely High BP Values (Pseudo-HTN)

- Too narrow cuff
- Obesity
- Thick calcified arteries (elderly, atherosclerosis, Monckeberg's sclerosis)

Note

- Wide cuff will give falsely low BP values.

Blood pressure waves

- Traube-Hering waves:** are fluctuations in BP synchronised with respiration.
- Cardiac waves:** These waves are due to systolic rise and diastolic fall.
- Mayer waves:** oscillations of BP seen in conditions like **hypotension**.

Regulation of BP

- Short-term regulation:** Rapidly acting *within seconds to minutes*.

1. Baroreceptor reflex

- Works when BP is in range **70-150 mmHg**
- Receptors are in **carotid sinus** and **aortic arch** wall.
- Stimulated by increased stretch (increased BP)
- Main response** is to **decrease BP** when stimulated; also decreases ventilation
- Baroreceptors are most sensitive to changes in **pulse pressure**.

2. Chemoreceptor reflex

- Works when BP is in range **40-70 mmHg**
- Receptors are in **carotid body** and **aortic body**
- Stimulated by hypoxia, hypercapnia and acidosis
- Main response** is to **increase ventilation**; also increases BP.

- **Afferent** for both the above reflexes: CN IX (sinus nerve of Hering) and CN X (vagus)
- **Centre** for reflex for both the above reflexes: **VMC** (Vasomotor centre) and **CIC** (Cardio-inhibitory centre, also known as cardiac vagal center) - both in the **medulla**.
- 3. **CNS ischemic response (Cushing's reflex)**
 - If the BP falls **below 40 mm Hg** the last ray of hope for survival is the CNS ischemic response; **ischemia of CNS directly stimulates VMC** due to increased pCO₂ and decreased pO₂ - this causes vasoconstriction and increase in BP.
- 4. **Hormonal release: Angiotensin II and ADH.**
- **Intermediate term** mechanisms (become active in 30 minutes - 1 hour)
 - Capillary fluid shift mechanism

- Stress relaxation and reverse stress relaxation
- **Long term regulation** (3-10 days)
 - **Renal** fluid conservation mechanism
 - Renin-angiotensin-aldosterone (RAA) system
- Among the above
 - **Most rapidly acting mechanism: Baroreceptor** >> chemoreceptor reflex
 - **Maximum BP increased by RAA system** >> CNS ischemic response.

Cushing's Reflex

- It is one form of **CNS ischemic response**
- When **intracranial pressure (CSF pressure)** is **increased**, the blood supply to the **VMC** (vasomotor centre) is compromised, and the local hypoxia and hypercapnia increase its discharge.
- The resultant **rise in systemic arterial pressure** tends to restore blood flow to the medulla. This rise in blood pressure causes a reflex decrease in heart rate (**reflex bradycardia**) via the arterial baroreceptors. **THIS** is why bradycardia, rather than tachycardia, is characteristically seen in patients with increased intracranial pressure.
- **Cushing's triad:**
 - Bradycardia,
 - Hypertension (with widened pulse pressure),
 - Respiratory depression (bradypnea).

Bainbridge Reflex

- Rapid infusion of blood or saline in anaesthetized animals sometimes produces a rise in heart rate **if the initial rate is low**.
- It appears to be **true reflex** rather than a response to local stretch.
- The receptors are **tachycardia producing atrial receptors** (TPAR) located in atrial wall where the vena cavae open into atria (veno-atrial junction).
- The reflex is abolished by vagotomy as the responses are mediated by vagus nerves.

Bezold-Jarisch Reflex (Coronary Chemoreflex)

- Injection of chemicals like capsaicin into left coronary artery produces hyperventilation, bradycardia, hypotension and coronary artery vasodilation.
- The receptors are chemoreceptors (**type C** nerve fibres) present in coronary arteries and ventricles.
- **Chemicals** which can trigger Bezold Jarisch's reflex include:
 - Endogenous: Serotonin, prostaglandins, histamine, bradykinin, adenosine.
 - Exogenous: Capsaicin, nicotine, veratrum alkaloids, snake and insect venoms.

Autoregulation

- The capacity of tissues to regulate their own blood flow despite changes in the BP within a certain range is called **autoregulation**.
- Autoregulation is strong in **heart** (ranges 60-200 mmHg); **brain** (ranges 65-140 mmHg); **kidney** (ranges 75-160 mmHg); moderate in GIT and skeletal muscle; little in skin and **NO autoregulation** in the **lung**.

Nitric Oxide

- See under inflammatory mediators under general pathology in pathology chapter (Pg.382).

Endothelins (ET)

- 3 types- ET1, ET2, ET3.
- **ET1** is the **most potent vasoconstrictor** agents produced by endothelial cells.
- ET ↓ renal blood flow and GFR and stimulates aldosterone.
- ↑ **Endothelin** levels in **HTN, CHF, angina**.
- Effects of ET1 are:
 - Vasoconstriction
 - Chronotropic
 - Inotropic
 - Bronchoconstriction
 - Decrease in GFR.

VASCULAR PHYSIOLOGY

BASICS OF HEMODYNAMICS

Ohm's Law

- Ohm's law for **electricity** is $I = E/R$, i.e., Current (I) = Electromotive force (E)/Resistance (R).
- This may be rewritten for the **vascular system** as $F = P/R$, i.e., Flow = Pressure/Resistance.

- **Blood flow to an organ** is directly proportional to perfusion pressure and inversely proportional to resistance.

Poiseuille-Hagen Formula

- This formula denotes the **relation between viscosity** of the fluid with **radius** and **length** of the tube.

$$F = (P_a - P_v) \times (\pi/8) \times (1/\eta) \times (r^4/L)$$

Where

- F = flow
- $P_a - P_v$ = pressure difference between both ends of the tube.
- η = viscosity of fluid
- r = radius of the tube
- L = length of the tube
- Calculation of **resistance** is also by the Poiseuille Hagen formula:

$$R = 8\eta L / \pi r^4$$

- Inference from the above equation:

- **Flow** $\propto r^4$ (i.e, if radius increases flow increases and vice versa)
- **Resistance** $\propto 1/r^4$ (i.e, if radius increases, resistance decreases and vice versa)

Radius (x)	Flow	Resistance
1/2x (half)	↓ 16 times	↑ 16 times
2x (doubled)	↑ 16 times	↓ 1/16 times (↓ to 6.25% of original value)
3x (trebled)	↑ 81 times	↓ 1/81 times (↓ to 1.2% of original value)
4x (quadrupled)	↑ 256 times	↓ 1/256 times (↓ to 0.3% of original value)

EXTRA EDGE

- Blood flow is **doubled** by an **increase in only 19% of the radius** of blood vessel.
- Question can be asked about "A **50% increase in radius**" — it will cause increase in blood flow by **5 times** (would appear as 1 and half 'x' or 1.5x in above table ($1.5^4 = 5.06$)).
- Question can also be asked about "A **50% decrease in radius**" — would correspond to 1/2x (half) in above table.

Types of Flow

Laminar flow	Turbulent flow
Silent	Noisy
Flow occurs in layers (streamlined)	No layers (flow is disturbed)
More efficient (less energy consumed)	Less efficient
Velocity is below critical velocity	Above critical velocity
Reynold's number is < 2000	Reynold's number is > 3000
Parabolic velocity profile: flow is maximum in centre of the vessel and goes on decreasing towards the vessel wall	No such gradient in flow from centre to periphery

Reynold's Number

- The **probability of turbulence** is expressed in terms of **Reynold's number**, which is calculated as

$$Re = \rho DV / \eta$$

Where

- Re = Reynold's number
- ρ = density of fluid
- D = diameter of the vessel
- V = velocity of flow
- η = viscosity
- Flow is **laminar** if $Re < 2000$; if $Re > 300$ flow is turbulent.
- **Examples** of turbulent flow : Korotkoff's sounds, heart murmurs, bruits.

Velocity

- Velocity (**critical velocity**) is the most important determinant of turbulent blood flow. For every artery, there is a velocity above which flow will become turbulent. Laminar flow occurs till critical velocity.
- Velocity is **inversely proportional** to **cross sectional area** (**inversely proportional to square of radius** of vessel, since $area = 2\pi r^2$).

$$V = Q/A$$

Where

- V = velocity
- Q = quantity/amount of fluid
- A = total cross sectional area.
- Therefore **velocity is maximum in aorta** (30-35 cm/sec) with **least cross-sectional area** and **minimum at level of capillaries** (0.2-0.3 mm/sec) with **maximum total cross sectional area**.
- **BP is maximum in aorta** and minimum in vena cava.
- Also **smaller vessels have laminar blood flow** due to lesser velocity.
- The average **arm to tongue circulation time** is **15 seconds**.
- The normal **arm to retina** circulation time is **12 seconds**.

EXTRA EDGE

- **Lateral pressure** in the blood vessels **determines the degree of perfusion** of tissues.
- **Bernoulli's principle:** the total pressure (static + dynamic) in a closed system always remains constant. The total of potential and kinetic energy at any given point in a system is constant.
- **Shear stress** is maximum in arterioles > capillary and minimum in large veins > vena cava.

FACTORS AFFECTING PERIPHERAL RESISTANCE

Radius of Blood Vessel

- ▶ Radius of blood vessel affecting peripheral resistance is called **vascular hindrance**.
- ▶ **Vasocanstriction** increases and **vasodilatation** decreases peripheral resistance.

Viscosity of Blood

- Viscosity of Blood affecting peripheral resistance is called **hematological hindrance**.
- **Hematocrit** is the **single most factor** that affects viscosity of blood.
- In plasma, it is the composition of **plasma proteins** that affects blood viscosity.
- When red cells become rigid as seen in **hereditary spherocytosis**, **viscosity increases**.
- **Increased body temperature** decreases viscosity and vice versa.
- **Plasma skimming**: In blood vessels, RBCs mostly accumulate at the centre of the column of flowing blood. Blood entering into smaller branches arising from large vessel mainly comes from peripheral part of column of blood - thus **smaller blood vessels contain less red cells** - this is **plasma skimming**!. This explains why **hematocrit of capillary blood is 25% lesser** than whole blood hematocrit.
- The pressure at which the blood flow through a vessel reduces to 'zero' (but pressure is not zero) is called **critical closing pressure**.

Law of Laplace

- ▶ This gives the relationship between the distending **pressure (P)**, the **tension (T)** in the wall of any structure and the **radius (r)**.
- ▶ This law states that the tension (T) in the all of a cylinder is equal to the product of the transmural pressure (P) and the radius (r) divided by the all thickness (w): **T = Pr/w**.

Law of Laplace

- ▶ Applications of Laplace's law:
 - **Capillaries do not rupture**, although they are thin walled.
 - **Work done by dilated heart is more** than non-dilated heart; a dilated heart pumps blood less efficiently.

BASICS OF VASCULAR SYSTEM

- **Endothelium** is present in all vessels including heart chambers and surface of valves.
- **Elastic tissue and smooth muscle** are present in all vessels **except venules and capillary**.
- **Outermost fibrous tissue** is present in all vessels **except capillary**.
- **Total cross sectional area** is minimum for aorta and **maximum for capillaries**.
- Maximum percentage of blood volume is in **venous system (capacitance vessels, 54%)** and minimum in arterioles (1%). Heart contains about 12%.
- **Velocity** of blood flow is **maximum in aorta** and least in capillaries
- **Arterioles** are the major sites of vascular resistance-distribution of blood flow is mainly regulated by arterioles.

Capillaries

- The **exchange of materials** (O₂, CO₂) between blood and tissue fluids takes place **ONLY** in capillaries - hence called **exchange vessels**.
- There is **NO** smooth muscle in the capillaries; they contain only a **single layer of endothelial cells** (tunica intima).
- **Total cross sectional area** of capillary network is **highest**.
- Capillaries contain about **5% of total blood volume**.
- **Most permeable capillaries** are in **glomerulus**; least permeable in **brain**.

Pericytes

- **Pericytes** are a/w capillaries in the **retina, lungs and skeletal muscles** - similar to mesangial cells in the glomeruli.
- They are contractile and they release vasoactive agents.

Types of Blood Vessels

Type	Examples	and Features
Windkessel vessels	Aorta and major vessels	They have a lot of elastic tissue ; show elastic recoil effect (windkessel effect) when stretched; have higher compliance
Resistance vessels	Arterioles	They have some elastic tissue and LOT of smooth muscle (have maximum wall thickness to lumen ratio); major site of peripheral resistance

Contd...

Contd

Type	Examples	and Features
Exchange vessels	Capillaries	No innervation ; controlled by pre-capillary sphincters
Capacitance vessels	Veins (venous system)	Normally 60% of total body blood is present in venous compartment
Shunt vessels	A-V anastomoses in fingertips and earlobes	They have thick muscular wall; very richly innervated

REGIONAL CIRCULATION

Important numbers

- ▶ **Total Blood flow in ml/min** (i.e., blood flow to whole organs in **maximum to minimum**): **Liver** (1500) > **Kidney** (1250) > **skeletal Muscle** (840) > **Brain** (750) > **Skin** (460) > **Coronary /Heart** (250). (mnemonic: "**Laalu Ki Maa BSC**")
- ▶ **Blood flow per unit mass in ml/100 gram/mln** (**maximum to minimum**): **Caratid body** (2000) > **Kidney** (420) > **Heart** (84) > **Liver** (57.7) > **Skin** (12.8) > **skeletal muscle** (2.7)
- ▶ **Oxygen consumption** per unit mass in mL/100g/min - **maximum in heart** 9.7 mL/100g/min.
- ▶ **Percentage of total cardiac output** (**maximum to minimum**): **Liver** (27.8%) > **Kidneys** (23.5%) > **Heart** (4.7%).

CEREBRAL CIRCULATION

- **Weight** of adult brain **1400 g** in air, but in the **CSF** it weighs only **50 g**.
- **Blood flow** of brain is **750 ml/min** (**14%** of cardiac output and **54 ml/100g/min**).
- **Blood flow** in the **grey matter** is about **4 times** that in the white matter.
- **Oxygen consumption** in brain is **3.5 mL/100g/mln** and is **20%** of total body oxygen consumption.
- Cerebral arteries are **end arteries**; capillaries in brain are **non-fenestrated**. The brain capillaries are surrounded by the end feet of **astrocytes** - forms the blood brain barrier (BBB).
- **Kety method** of measuring cerebral blood flow uses **nitrous oxide**; it is based on **Flick's principle**.
- The volume of blood, CSF and brain in the cranium at any time must be relatively constant (**Monro-Kellie doctrine**).
- In the brain autoregulation maintains a normal cerebral blood flow at arterial pressures of **65-140 mm Hg**.
- **Respiratory quotient**, of cerebral tissue is **0.95-0.99** in normal individuals.
- **CO₂** is a potent **cerebral vasodllator** and major controller of **cerebral blood flow**.

- Brain tissue is highly **sensitive to hypoxia**; stoppage of blood flow for more than **5 minutes** causes irreparable damage (coma).
- Brain utilises **glucose** as the main fuel (**independent of insulin**).
- The **part of the brain with the largest blood flow** is the **inferior colliculus**.

CORONARY CIRCULATION

- Coronary arteries are **end arterles**; there is no anastomoses between right and left coronary arteries.
- Blood flow to heart at rest is **250 mL/mln** (**84 mL/100g/mln.**); **about 5%** of total cardiac output.
- Most of coronary blood flow (**> 70%**) **occurs during diastole** since cardiac muscle relaxes.
- **Oxygen consumption** of normal beating heart is **9.7 mL/100g/min** (**highest** in the body).
- Myocardium has **highest A-V oxygen difference** among all organs. (**heart extracts 80% of oxygen from arterial blood** compared to whole body average of 25% extraction!)
- Coronary blood flow is **directly proportional to perfusion pressure** and **inversely proportional to vascular resistance**.
- **Chemical autoregulation** (by local metabolites) is **most important** in regulating coronary blood flow (than neural regulation).
- **Adenosine** is the major **coronary vasodilator** during hypoxic states (**Berne's hypothesis**).
- Cardiac **muscle contraction** accounts for **75%** of energy use and basal metabolism (cellular processes) accounts for the remaining 25% of energy use.
- The **external work** done by the left ventricle in one beat = **stroke work** = **afterload (pressure) X stroke volume** = (93 mm Hg × 90 mL).

PULMONARY CIRCULATION

- Pulmonary circulation is a **low-pressure, low-resistance** (**1/10th** the systemic vascular resistance), **high compliance** vascular bed.
- Pulmonary artery systolic and diastolic pressure is **25/10 mm Hg** (**mean 15 mm Hg**).

- Normal pulmonary blood flow is **equal to right ventricular output** = 5 l./min.
- Pulmonary **blood volume** is approximately **1 litre** which is located mainly in the pulmonary artery and veins.
- In the lungs, **capillary flow is pulsatile**.
- In the lungs, **hypoxia causes vasoconstriction**.
- Blood flow is **lowest at apex** of the lung (**zone 1**) and **highest at the base (zone 3)**; **Zone 1** acts as **physiological dead space**.
- During exercise, blood flow increases in all parts of the lungs (4-7 fold) by **opening up of inactive capillaries**.
- The ability of the lungs to accommodate greatly increased blood flow during exercise **without increasing the pulmonary arterial pressure** conserves the energy of the right side of the heart.
- It takes an RBC about **0.75 seconds** to **traverse the pulmonary capillaries at rest** and **0.3 seconds or less** during exercise.

RESPIRATORY PHYSIOLOGY

REGULATION OF PULMONARY CIRCULATION

- Local **hypoxia** produces **vasoconstriction in pulmonary vessels** (opposite to that which occurs in the systemic circulation).
- **Chemical control** is more important than neural control of pulmonary vessels. Effects of various stimuli is given below.

Vasodilation	Vasoconstriction
<ul style="list-style-type: none"> • Nitric oxide • Prostacyclin • PGE₂ • Bradykinin • Acetylcholine • Atrial natriuretic peptide • Vasopressin • Substance P • VIP 	<ul style="list-style-type: none"> • Hypoxia • Hypercapnia • Angiotensin II • Thromboxane A₂ • Leukotrienes (LTC₄, LTD₄) • Endothelins • Histamine • Norepinephrine • Serotonin

Ventilation : Perfusion Ratio (V/Q ratio)

- The ratio of alveolar ventilation (V) to pulmonary blood flow (Q) is the **V/Q ratio**.
- For the whole lung, at rest, V/Q ratio = **0.8**.
- In **upright posture**, base of the lung is better ventilated and also better perfused compared to apex.
- BUT the **blood flow exhibits a 5-fold difference** between apex and base of lung, whereas **ventilation exhibits a 2-fold difference**.
- V/Q ratio = **"0.6 at the base"** and **"3.6 at the apex"** of the lung.
- Since **V/Q is high at the apices** of the lungs, **TB occurs more commonly at apex** since high oxygen level at apex favors growth of Mycobacterium tuberculosis.

BASICS OF AIRWAYS

- Anatomy of airways and inspiratory and expiratory muscles have been covered in "thorax" section in "Anatomy" Chapter (Pg 68).

- Normal respiratory rate (adult): 12-15 times per minute
- At rest: **250 ml of oxygen enters** the body per minute and **200 ml of CO₂ is excreted**
- Composition of dry air : **20.98% O₂, 78.6% N₂, 0.04% CO₂, 0.92% of inert gases** such as argon and helium
- **Lymphatic channels are more abundant in the lungs** than in any other organ.
- There is a **circadian rhythm in bronchial tone**, with **maximal constriction at about 6 AM** and maximal dilatation at 6 PM. **That is why asthma attacks are more severe in the late night and early morning hours**

PRESSURES IN THORACIC CAVITY

Intrapleural Pressure

- This pressure within pleural space (also known as **intrathoracic pressure**); since intrapleural pressure reflects **mid thoracic esophageal pressure**, in practice it is measured by recording **intra-esophageal pressure**.
- Intrapleural pressure is **negative during quiet breathing (-5 cm H₂O)** and more negative during **deep inspiration (-8 cm H₂O)** and during **forced inspiration** it may be **-30 cm H₂O**.
- BUT during **forced expiration** intrapleural pressure becomes **positive**.
- Why is the intrapleural pressure negative? - the pleural space is a relative vacuum. The lungs have the tendency to collapse and the chest wall has tendency to expand. Therefore **elastic recoil** effects of lungs and chest wall are **exerted equally in opposite directions**. These equal and opposing forces cause the intrapleural pressure to be negative (less than atmospheric pressure).
- ALSO, one extra point to understand is that — **During both inspiration and expiration, intrapleural pressure is negative** - this was asked as an MCQ in WBPB 2015.

Alveolar Pressure

- It is the pressure **within the alveoli**; during **inspiration** it is **-1 mm Hg** and during **expiration** it is **+1 mm Hg**.

Transmural Pressure

- **Transpulmonary pressure**: Pressure difference across the lung wall; measured by **subtracting intrapleural from alveolar pressure**; this is the pressure that **keeps the lung inflated** and prevents the lungs from collapsing. Transpulmonary pressure is **always positive** in normal breathing. At the end of expiration it is **+5 cm H₂O** and at the end of inspiration it is **+8 cm H₂O**.
- **Transairway pressure**: pressure difference between the inside and outside of the airway.

LUNG COMPLIANCE

- **Lung compliance** is a measure of its **distensibility**. It means the ability to stretch (**stretchability**).
- It can be assessed by the **pressure-volume curve**.
- Compliance is defined as the **change in volume (ΔV)** per unit **change in pressure (ΔP)**.
- Compliance = **ΔV/ΔP**.
- **Static compliance**: It is the measurement made without taking into account the effect of the different phases of respiration.
- **Dynamic compliance**: Compliance measured during the different phases of respiration.
- **Specific compliance** = Compliance / FRC.
- **Normal compliance** of human lung = **200 ml/cm H₂O** (indicates that 1 cm H₂O pressure change will cause 200 mL lung volume change).
- The compliance of lung and chest wall together (respiratory system compliance) is normally **70-85 cm H₂O**.

Factors affecting Lung compliance

- Lung size: **Smaller the lungs, lesser** the compliance.
- Lung volume: Compliance is **low at high lung volumes** and **high at low lung volumes**.
- Compliance is **more during deflation** rather than during inflation.
- If **surface tension is more, compliance is less**.

Increased lung compliance Decreased lung compliance

<ul style="list-style-type: none"> • COPD (Emphysema) • Old age 	<ul style="list-style-type: none"> • Restrictive lung diseases • Pulmonary fibrosis • Pulmonary congestion (increased pulmonary venous pressure) • Decreased surfactant
---	---

EXTRA EDGE

- Compliance (distensibility) is **inversely proportional** to elasticity/elastic recoil. **Elasticity** refers to the tendency for something to **oppose stretch or distortion**, as well as its ability to **return to its original configuration** after the distorting force is removed.
- So in **emphysema** there is **increased compliance** (lung is easily inflated) but there is **less elasticity**/elastic recoiling force leading to **difficulty in getting air out of the lungs** - thus emphysematous lungs have **abnormally high residual volume**.

SURFACTANT

- Surfactant is a mixture of **lipids (90%)**; proteins (8%) and carbohydrates (2%).
- **Main lipid (62%) is dipalmitoyl lecithin** (lecithin is also called **phosphatidylcholine**).
- Surfactant is secreted by **type II pneumocytes** (lamellar bodies contain surfactant).
- Surfactant production **starts at 20-24 weeks** of fetal life.
- Surfactant production **matures between 35-37 weeks**.
- It appears in **amniotic fluid between 28-32 weeks** of gestation.
- Functions of surfactant:
 - Prevents alveolar collapse.
 - Prevents pulmonary edema.
 - Decreases work of breathing.

AIRWAY RESISTANCE

- The **major site of airway resistance** is the **medium sized bronchi** (lobar and segmental) and **bronchi down to the seventh generation**.
- **Smaller airways** contribute **only 10-15%** to the total airways resistance since their total cross sectional area is large (as in capillaries) and they are aligned parallel.
- If **radius decreases by half, resistance increases 16 times** (as per Poiseuille's formula) - **similar as in capillaries**.

Increased airways resistance Decreased airway resistance

<ul style="list-style-type: none"> • Bronchoconstriction • Parasympathetic (vagal cholinergic fibres) • During expiration (due to dynamic compression of airways) • More density/viscosity of inspired air • At higher lung volumes 	<ul style="list-style-type: none"> • Branchodilation • Sympathetic (adrenergic fibres) • During inspiration • Less dense air (ex - oxygen-helium mixture as given to deep sea divers and in treating status asthmaticus) • At lower lung volumes
---	---

WORK OF BREATHING

- **Elastic work** (compliance work) accounts for 65% of work done, the major work of *inflating the lung* against elastic resistance of chest wall and lungs.
- **Non-elastic work** (accounts for 35%) work done to overcome
 - Viscous resistance of lungs (7%)
 - Airways resistance (28%)
- **Work** = $\Delta P \times \Delta V$ (change in intrapleural pressure \times change in lung volume)
- Since in quiet breathing, *expiration is a passive process*, NO work is done during expiration.
- **Total work of breathing** during quiet respiration in normal person is **0.3–0.8 kg/min**. It represents 2–3% of resting oxygen consumption.

EXTRA EDGE

- In **restrictive lung disease**, patient has to overcome higher resistance for normal tidal breathing - more work has to be done by respiratory muscles for inspiration. This can be minimized by **rapid and shallow breathing** - of course, the tidal volume is decreased BUT the increased respiratory rate ensures adequate ventilation of lungs!
- Opposite to this occurs in **obstructive lung disease** to decrease the work of breathing, i.e., by **slow and deep breathing**.

Dead space

- **Anatomic dead space**: Volume of **conducting airways**, approximately = **150 cc**.
- The **anatomic dead space** can be measured by
 - **Single breath nitrogen washout method (Fowler's method)**.
 - Radford's formula (Normally the **volume of dead space is equal to the body weight in pounds**)
 - Single breath CO_2 method
- Normally, dead space: tidal volume ratio is **0.3** (150 mL: 500 mL)
- **Physiologic dead space**: Volume that DOES NOT participate in gas exchange.
- The physiologic dead space is determined by tidal volume and concentration of CO_2 in alveolar and mixed expired air - by **Bohr's mixing equation**.
- In **healthy individuals**, both the anatomic and physiologic dead spaces **are equal**.

LUNG VOLUMES AND CAPACITIES

- **Static lung volumes and capacities**: Time factor is not involved; expressed in mL or L.
- **Dynamic lung volumes and capacities**: Time dependent; expressed in mL/min or L/min.

Static Lung Volumes and Capacities

Measurement	Definition	Value
Lung Volumes		
Tidal volume (TV)	Amount of air that is inhaled or exhaled in one breath during relaxed quiet breathing	500 mL
Inspiratory reserve volume (IRV)	Maximum volume of air that can be inspired at the end of a normal tidal inspiration	3000 mL
Expiratory reserve volume (ERV)	Maximum volume of air that can be forcibly expired after a normal tidal expiration	1000 mL
Residual volume (RV)	Volume of air remaining in lungs after maximal voluntary expiration	1000 mL
Critical closing volume	Volume of air above the residual volume at which the airways in the lower dependant part of lungs begin to close off (small airways begin to collapse)	Close to RV
Lung Capacities		
Inspiratory capacity (IC)	Maximum volume of air that can be inspired at the end of a normal tidal expiration. $\text{IC} = \text{IRV} + \text{TV}$	3500 mL
Functional residual capacity (FRC)	Volume of gas remaining in the lung after a normal tidal expiration. $\text{FRC} = \text{ERV} + \text{RV}$ At FRC, the opposing elastic recoil forces of the lungs and chest wall are in equilibrium and there is no exertion by the diaphragm or other respiratory muscles	2500 mL

Contd...

Contd

Measurement	Definition	Value
Vital capacity (VC)	Maximum volume of air that can be expired after a maximal inspiration. Values increase with size and decrease with age. Approx. 80% of total lung capacity. $\text{VC} = (\text{IC} + \text{ERV})$ or $(\text{IRV} + \text{TV} + \text{ERV})$	4500 mL
Total lung capacity	Total volume of the lung following a maximal inspiration. $\text{TLC} = \text{IRV} + \text{TV} + \text{ERV} + \text{RV} = \text{VC} + \text{RV}$	5500 mL
Closing capacity	Sum of residual volume and closing volume.	

EXTRA EDGE

- All above volumes and capacities can be measured by simple **spirometry**, except **RV, FRC and TLC**; for these the other methods used are:
 - Nitrogen washout method
 - Helium dilution method
 - Body plethysmography (**best method**).

Dynamic Lung Volumes and Capacities

Measurements	Comments
Forced vital capacity (FVC) or timed vital capacity	The volume of gas that can be forcefully expelled from the lungs after maximal inspiration; similar to VC, BUT it is rapid and forceful exhalation. FVC is an index of flow rate . Components of FVC are: Forced expiratory volume in 1s (FEV1) : Volume of FVC expelled in the first second of exhalation; normally it is 80% of the FVC; i.e. $\text{FEV}_1/\text{FVC} = 0.8$ FEV2 : Volume of FVC expelled in 2 sec of exhalation; normally 95% FEV3 : Volume of FVC expelled in 3 sec of exhalation; normally 97% FEV1 is the single most useful test to detect generalised airway obstruction
Maximum mid expiratory flow rate (MMEFR)	Forced expiratory flow from 25–75% of the FVC – $\text{FEF}_{25-75\%}$ (during the middle 50% of the FVC). This indicates patency of smaller airways (more sensitive than PEFr)
Peak expiratory flow rate (PEFR)	The maximal air flow rate/velocity (L/min) achieved in the FVC maneuver. Normal value is 400–600 L/min or 6–10 L/sec; measured using a peak flow meter
Respiratory minute Volume (MV) or Pulmonary ventilation (PV)	Tidal volume (TV) \times Respiratory rate (RR) = $500 \times 12 = 6000 \text{ mL/min}$ (6 L/min)
Alveolar ventilation	Alveolar ventilation = $(\text{TV} - \text{dead space}) \times \text{RR} = (500 - 150) \times 12 = 4.2 \text{ L/min}$.
Maximum Voluntary ventilation (MVV)	Also known as Maximum Breathing Capacity; the maximum volume of air that can be breathed per minute by maximal voluntary effort; It is 125–170 L/min.
Dyspneic index or Breathing reserve or pulmonary reserve	Dyspneic index is the percentage of respiratory capacity not being used at a given respiratory minute volume. It is expressed as percentage of MVV = $(\text{MVV} - \text{PV})/\text{MVV} \times 100$ Normal dyspneic index is $> 60\text{--}70\%$; if $< 60\%$, dyspnea is present

Obstructive Vs Restrictive Lung Disease

Contd...

	Obstructive	Restrictive parenchymal		Obstructive	Restrictive parenchymal
TLC	Normal	↓	VC	↓	↓
FRC	↑	↓	FEV1	↓↓	↓
RV	↑	↓	FEV1/FVC	↓	Normal or ↑

Contd...

EXTRA EDGE

- Inferences from the above table are:
 - Obstructive** lung volumes > normal (\uparrow TLC, \uparrow FRC, \uparrow RV);
 - Restrictive** lung volumes < normal (\downarrow TLC, \downarrow FRC, \downarrow RV).
 - In **both** obstructive and restrictive, **FEV1 and FVC are reduced**, but in **obstructive**, **FEV1 is more dramatically reduced**, resulting in a \downarrow **FEV1/FVC ratio** (ratio normal or \uparrow in restrictive).
 - RV increased** in restrictive extra-parenchymal.

Common Respiratory Diseases by Diagnostic Categories

Obstructive	Restrictive - parenchymal	Restrictive - extraparenchymal
Asthma COPD (chronic bronchitis, emphysema) Bronchiectasis Cystic fibrosis Bronchiolitis	Sarcoidosis Idiopathic pulmonary fibrosis Pneumocystosis Drug or radiation-induced interstitial lung disease	Neuromuscular Diaphragmatic weakness/paralysis Myasthenia gravis Guillain-Barré synd. Muscular dystrophies Cervical spine injury Chest wall Kyphoscoliosis Obesity Ankylosing spondylitis

GAS EXCHANGE IN LUNGS

Diffusion Gradient

- Gas exchange at the level of lungs and tissue occurs via simple diffusion process.
- Diffusion of gases depends on the *partial pressure of gases across the alveolar-capillary membrane - diffusion gradient*.
- Oxygen** diffuses easily across the membrane because of the greater difference in PO_2 between the alveoli (160 mmHg) and the arterial blood (60 mmHg); hence the diffusion gradient for oxygen is **60 mmHg**.
- The diffusion gradient for CO_2 across the alveolar-capillary membrane is **6 mmHg** (much lower than that of oxygen).

Diffusion Capacity of Lung

- Diffusion capacity** of lung is defined as the volume of gas diffusing across the respiratory membrane in 1 minute when the pressure gradient is 1 mmHg.
- It provides a measure of the **rate of gas transfer** in the lungs (ability of the lungs to transfer gas from inhaled air to RBCs in pulmonary capillaries)

- Diffusion coefficient** of a gas is directly proportional to its solubility (S) and inversely proportional to square root of its molecular weight (MW). (S/\sqrt{MW}). Thus a **highly soluble molecule** or a **small molecule** will **diffuse rapidly**.
- For example, diffusion coefficient of CO_2 in aqueous solutions is **20 times greater than that of oxygen** because of its higher solubility, even though it is a larger molecule than O_2 .
- Diffusion coefficient for different gases are:
 - Oxygen = 1
 - CO_2 = 20.3
 - CO = 0.81
 - Helium = 0.95
 - Nitrogen = 0.53

Perfusion and Diffusion Limited Gas Exchange

Perfusion limited gas	Diffusion limited gas
<ul style="list-style-type: none"> N_2, O_2, CO_2. Gas exchange across alveolar-capillary barrier is limited by blood flow through pulmonary capillaries (perfusion). The only way to increase its uptake is to increase the amount of blood flow through the alveolar capillaries. 	<ul style="list-style-type: none"> Carbon Monoxide (CO). Gas exchange across alveolar-capillary barrier is limited by diffusion process. Net diffusion into pulmonary capillary depends on magnitude of partial pressure gradient.

Diffusion Capacity of Carbon Monoxide (DLCO)

- DLCO = Single-breath** diffusing capacity of Lung. For carbon monoxide, DLCO is taken as an **index of diffusion capacity**.
- This test uses a small (and safe) amount of carbon monoxide (CO) to measure gas exchange across the alveolar membrane during a **10-sec** breath hold.
- CO in exhaled breath is analyzed to determine the quantity of CO crossing the alveolar membrane and combining with hemoglobin in red blood cells.
 - CO is used** to determine the lung diffusing capacity because:
 - CO uptake is **limited by diffusion** and not by blood flow
 - There is **essentially no CO in venous blood**
 - The **affinity of CO for Hb is 210 times greater** than for oxygen - which causes the partial pressure of CO to remain essentially zero in the pulmonary capillaries

Decreased DLCO

- Interstitial lung disease (sarcoidosis, connective tissue diseases)
- Pulmonary fibrosis
- emphysema (destroyed alveolar membranes)
- Pulmonary hypertension (curtailed pulmonary vasculature)
- Anemia (reduce alveolar capillary hemoglobin).

Increased DLCO

- Asthma.
- Acute congestive heart failure
- Polycythemia
- Pulmonary alveolar hemorrhage
- Obesity
- High altitude
- Left to right cardiac shunting

Physiologic Shunt

- Partial pressure of oxygen in **arterial blood** is **95-98 mm Hg**, which is less than **alveolar oxygen** partial pressure of **100-104 mm Hg**.
- This is because, in the bronchial circulation, **deoxygenated venous blood directly drains into the oxygenated blood of pulmonary veins** that accounts for **physiologic shunt**.
- Also NOTE: pO_2 of inhaled (atmospheric) air is 160 mm Hg.

OXYGEN TRANSPORT

- Oxygen transport occurs through two processes
 - Oxygen **bound to Hb (98%)**
 - Dissolved Oxygen (2%)**
- O_2 **content** = (O_2 binding capacity \times % saturation) + dissolved O_2 .

Dissolved Oxygen

- The amount of physically dissolved oxygen in blood can be predicted by **Henry's law**: states that "the amount of gas that dissolves in a liquid at a given temperature is proportional to the partial pressure of the gas".
- At PaO_2 of 95 mm Hg, the **dissolved oxygen** is **0.3 ml/dl** meaning in a normal healthy adult, 0.3 ml. of oxygen is transported in dissolved form in 100 ml. of blood.
- As **cardiac output is 5 L/min**, at rest **total oxygen transported in dissolved form is 15 ml/min** - grossly inadequate for **oxygen requirement** of the body which is **250 ml/min** at rest.

EXTRA EDGE

- In **hyperbaric oxygen therapy**, the **dissolved oxygen increases to 6 ml/dl** of blood which accounts for total oxygen supply of **300 ml/min**, which is adequate for tissue oxygenation.

Oxygen Bound to Hb

- At PaO_2 of 95 mm Hg, **97% of Hb** is saturated with oxygen.
- 1 g Hb** can bind **1.34 ml. O_2** .
- Normal Hb amount in blood is 15 g/100 ml. Thus 100 ml of blood can bind $(15 \times 1.34) = 20.1$ ml of oxygen
- Thus **O_2 binding capacity = 20.1 ml. O_2 /dL**
- BUT when Hb is **100% saturated** with O_2 , Hb binds **1.39 ml** of O_2 per gram of Hb - this is known as **oxygen capacity (O_2 cap)** of hemoglobin.
- In venous blood, at PvO_2 of 40 mm Hg, Hb is only 75% saturated. Thus 100 ml of venous blood would carry 14.4 ml. of O_2 .

EXTRA EDGE

- Oxygen extraction ratio** = (Oxygen extracted by tissue/ Amount of Oxygen delivered) \times 100 OR (Consumption/ supply) \times 100.
- It is the **amount of oxygen taken up by the tissues** from blood.
- In **cardiac muscle**, OER may be as high as **85%**.

OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

- The relationship between the % **saturation of Hb** and **partial pressure of O_2** in arterial blood.
- Sigmoidal shaped** curve due to **positive cooperativity**, i.e. the binding of one molecule of O_2 facilitates the binding of the next. Similarly the release of one O_2 molecule promotes the release of others.
- p50** - it is the partial pressure of oxygen at which **Hb is 50% saturated** In **arterial blood** it is 26 mmHg and in **venous blood** it is 29 mm Hg.
- Remember the following points on the curve as in table below

pO_2 (partial pressure of oxygen)	SO_2 (oxygen saturation of Hb)
0 mm Hg	0% (origin of curve)
26 mm Hg	50% (p50)
40 mm Hg	75% (normal mixed venous blood)
pO_2 (partial pressure of oxygen)	SO_2 (oxygen saturation of Hb)
60 mm Hg	90%
95 mm Hg	97% (normal arterial blood)
100 mm Hg	98% (fully saturated arterial blood)

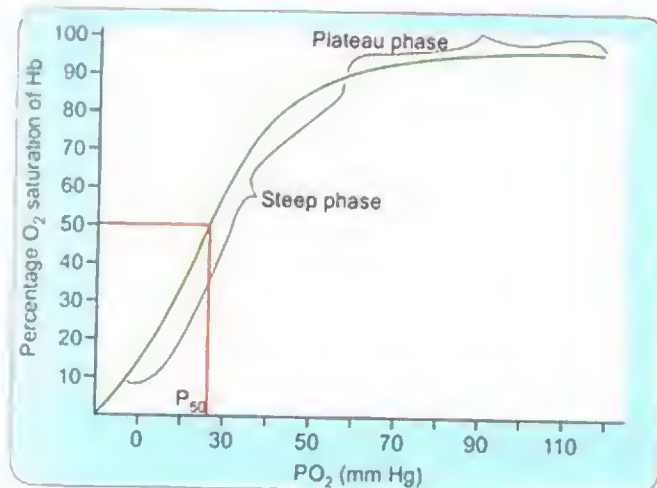


Fig. 3.9: Oxygen-hemoglobin dissociation curve. Note, at PO_2 of 27 mm Hg, Hb saturation of oxygen is 50% (P_{50}). Hb is 89% saturated with oxygen at PO_2 of 60 mm Hg, above which increase in Hb saturation is marginal that results in plateau phase of the curve

Effects on Oxy-Hb curve

- **Effect of pH:** Right shift of the oxy-Hb curve due to decreased pH (mainly) and rise in blood CO_2 (partly) is called the **Bohr effect**. The affinity of Hb for oxygen increases at higher pH, and decreases with fall in pH.
- **Double Bohr effect** occurs in the **placenta** since Bohr effect occurs in maternal as well as fetal tissue.
- **2, 3-DPG** is synthesized in the RBCs from metabolites of the **anaerobic glycolytic** pathway (since **RBCs lack mitochondria**). It binds to Hb stabilizing the deoxy form, and **reduces the affinity of Hb for O_2** , causing the **release of O_2** . Production of 2,3-DPG is **stimulated by hypoxia**, e.g. anemia and high altitude.

Shift of curve to right (Hb easily releases O_2) "Right shift Releases"	Shift of curve to left (Hb does not release O_2 easily, leading to tissue hypoxia)
$\uparrow PCO_2$ Anemia; high Altitudes; Acidosis (\downarrow pH) \uparrow 2, 3-DPG Exercise \uparrow Temperature (acidosis) Right shift ("CADET face Right!")	$\downarrow PCO_2$ \downarrow 2, 3-DPG \downarrow Temperature \uparrow pH (alkalosis) Fetal Hb (HbF) Methemoglobin and carboxyhemoglobin Rare hemoglobinopathies (Chesapeake and Heathrow)

Effects of Myoglobin

- Myoglobin is the Hb pigment in muscle
- Myoglobin binds only **one mole** of oxygen per mole.
- It shows **NO Bohr effect**.

- Myoglobin shifts oxy-Hb curve to **the left** and the curve loses sigmoid shape and becomes a **rectangular hyperbola**.
- p_{50} of myoglobin is **only 5 mm Hg** (compared to p_{50} of Hb which is 26 mm Hg).

Effects of Carbon Monoxide (CO)

- CO binds to Hb to form **carboxyhemoglobin**.
- The affinity of **Hb for CO is 210 times greater** than it is for O_2 (so even minor amounts of CO greatly reduce the capacity of Hb to bind O_2).
- Effects of CO are:
 - Decreases O_2 carrying capacity of blood
 - Shifts the oxy-Hb curve to the **left**
- **CO poisoning** causes **anemic hypoxia** since almost all Hb binds to CO and Hb is practically not available for O_2 transport.
- Treatment of CO poisoning is **100% oxygen** inhalation (helps to displace CO from Hb).

CO_2 TRANSPORT

CO_2 is transported in blood in 3 forms

1. Physically Dissolved in Plasma (7%)

- The **solubility co-efficient of CO_2** = 0.06 mL/dL/mm Hg (**20 times that of oxygen** i.e., 0.003 mL/dL/mm Hg).
- This in venous blood, **2.76 mL/dL** of CO_2 (46 mm Hg PCO_2 in venous blood \times 0.06) is carried in simple solution.

2. As Carbamino Compound (23%)

- Carbamino compounds with plasma proteins
- Carbamino-Hb in RBCs

3. As Bicarbonate Ions in Plasma and RBCs (70%)

- From tissues as soon as CO_2 is released into plasma, a bulk of it **diffuses into RBCs** and forms **carbonic acid**.
- $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
- This reaction normally proceeds slowly BUT the **RBC contain very high levels of enzyme carbonic anhydrase** which accelerates the conversion (**5000 times!**).
- The HCO_3^- diffuses out of RBCs in exchange for Cl⁻ via **anion exchanger 1** (earlier called **band-3** exchanger) - This process is called **chloride shift**-also called **Hamburger shift** (since discovered by Mr. Hamburger).
- Cl⁻ accumulates in RBC-it osmotically imbibes water and **increases RBC size** in venous blood. Hence **hematocrit of venous blood is 3% more** than arterial blood.

- Chloride shift occurs rapidly **within 1 second**.
- **CO_2 dissociation curve** is almost a **linear curve**.

Haldane Effect

- When blood passes through pulmonary capillaries, oxygen diffuses into blood to form oxy-Hb.
- Oxygenation of Hb shifts the CO_2 dissociation curve to the right and Hb begins to lose CO_2 .
- Thus in the lungs, loading of O_2 facilitates unloading of CO_2 - **Haldane effect**.

HYPOXIA

Hypoxic hypoxia	<ul style="list-style-type: none"> • Decreased arterial PO_2 • MC type of hypoxia seen clinically; MC cause is ventilation perfusion mismatch; also seen in hypoventilation (COPD) and right to left shunts. • May also be due to high altitude, hypoventilation, diffusion defect (pulmonary edema, lung fibrosis, lung collapse) • Oxygen therapy with 100% oxygen is useful
Anemic hypoxia	<ul style="list-style-type: none"> • Arterial PO_2 is normal. • Decreased O_2 carrying capacity of blood (amount of Hb available to carry O_2 is decreased) • Seen in anemia, CO poisoning, methemoglobinemia • hyperbaric oxygen therapy is useful
Stagnant hypoxia (Ischemic hypoxia)	<ul style="list-style-type: none"> • Decreased rate of blood flow to tissue so that adequate O_2 is not delivered to it despite a normal arterial PO_2 and Hb concentration - cyanosis is prominent feature. • A-V (arterial-venous) oxygen difference is maximum. • Seen in heart failure, shock, hemorrhage
Histotoxic hypoxia	<ul style="list-style-type: none"> • \downarrow Utilization of O_2 by tissues; the amount of O_2 delivered to a tissue is adequate but because of the action of a toxic agent (e.g. cyanide poisoning, diphtheria), the cells cannot make use of the O_2 supplied to them • O_2 therapy is NOT useful; hyperbaric oxygen therapy is useful

Hyperbaric Oxygen Therapy

- This is given by administering **100% oxygen** at increased pressure (**2000 mm Hg or 3 atmospheres**). This achieves **6 mL/dL** of dissolved oxygen.
- Indications are:
 1. **Air or gas embolism** (includes **diving-related**, iatrogenic, and accidental causes)

2. **Carbon monoxide poisoning**.
3. Clostridial myositis and myonecrosis (anaerobic gas gangrene)
4. **Crush injury, compartment syndrome**, and acute traumatic ischemias
5. Decompression sickness
6. Arterial insufficiency
7. Central retinal artery occlusion (**CRAO**)
8. Enhancement of healing in selected problem wounds (**diabetic ulcers**)
9. Exceptional blood loss (where transfusion is refused or impossible)
10. Intracranial abscess
11. Necrotizing soft tissue infections (e.g., **Fournier's gangrene**)
12. Osteomyelitis (refractory to other therapy)
13. Delayed **radiation injury** (soft-tissue injury and **bony necrosis**)
14. Skin grafts and flaps (compromised)
15. Thermal burns
16. Sudden sensorineural hearing loss

REGULATION OF RESPIRATION

- Two separate neural mechanisms regulate respiration.
 - Voluntary system = is located in the cerebral cortex.
 - The automatic system = is located in the **pons** and **medulla**.
- 1. **Medullary respiratory center:**
 - **Dorsal respiratory group (DRG):** Primarily **responsible for inspiration**; input via cranial nerves (**CN X**, peripheral chemoreceptors and mechanoreceptors in the lung) and **CN IX** (peripheral chemoreceptors) output via the **phrenic nerve**.
 - **Ventral respiratory group (VRG):** Primarily **responsible for active expiration during forceful breathing**; not active during normal breathing when expiration is passive. VRG has 3 regions
 - Rostral expiratory region (Botzinger complex)
 - Caudal expiratory region
 - Middle inspiratory region
 - ("**DIVE**" = **Dorsal Inspiration, Ventral Expiration**")
 - **Central pattern generator:** Present in the **Pre-Botzinger complex**; A group of pacemaker cells responsible for generating normal **respiratory rhythm**.
- 2. **Pontine respiratory centers:**
 - **Apneustic center:** In the lower pons, **stimulates inspiration**, producing **deep and prolonged inspiratory gasp**. It is tonically inhibited by **pneumotaxic center**.

- **Pneumotaxic center:** is located in the **nucleus parabrachialis medialis** and **Kolliker Fuse** nucleus that is present in the rostral **pons**. It coordinates respiration by switching between inspiration and expiration.

3. **Cerebral cortex:** Controls the voluntary component of breathing (i.e., a person can voluntarily hold breath or hyperventilate).

EXTRA EDGE

- Medullary lesions can lead to various type of abnormal breathing patterns which include Cluster breathing, Ataxic breathing (Biot's breathing), Cheyne-Stokes respiration, Gasping.

Reflexes Related to Respiration

- **Hering Breur inflation reflex:** is an increase in the duration of expiration produced by steady lung inflation and
- **Hering-Breuer deflation reflex:** is a decrease in the duration of expiration produced by marked deflation of the lung.
- **Pulmonary chemoreflex:** is due to the stimulation of J (juxtacapillary) receptors, which are actually C fibre endings, by hyperinflation of the lung or intracardiac administration of capsaicin. The reflex response that is produced is apnea followed by rapid breathing, bradycardia and hypotension.

Different Patterns of Breathing

Pattern	Description	Causes
Biot's respiration	3-4 cycles of normal respirations is followed by abrupt onset of apnea	Meningitis, morphine poisoning, brainstem damage
Apneusis	There is complete cessation of involuntary breathing, leading to respiratory arrest during sleep (Ondine's curse).	Lower pons
Kussmaul's breathing	Rapid and deep respiration "air hunger", tachypnea and hyperpnea	Diabetic ketoacidosis

Cheyne-Stokes Respiration/Periodic respiration/Cyclic Respiration

- This is common in **advanced Heart Failure** and is usually **a/w low cardiac output**.

- It is also seen in **uremia, brain diseases, during deep sleep** in some people.
- It is caused by a ↓ **sensitivity of the respiratory center to arterial PCO₂**
- There is an apneic phase, during which the arterial PO₂ falls and the arterial PCO₂ rises. These changes in the arterial blood gas content stimulate the depressed respiratory center, resulting in hyperventilation and hypocapnia, followed in turn by recurrence of apnea.
- It may be perceived by the patient or the patient's family as severe dyspnea or as a transient cessation of breathing.

PHYSIOLOGIC ADAPTATIONS TO HIGH ALTITUDE

Physiologic adaptations to high altitude

- Acute ↑ in ventilation (hyperventilation)
- Chronic ↑ in ventilation
- ↑ Erythropoietin → ↑ hematocrit and Hb (chronic hypoxia)
- ↑ 2,3-DPG (binds to Hb so that Hb releases more oxygen)
- Cellular changes (↑ mitochondria)
- ↑ renal excretion of bicarbonate (e.g., can augment by use of acetazolamide) to compensate for the respiratory alkalosis
- Chronic hypoxic pulmonary vasoconstriction results in RVH.

MORE HIGH YIELD POINTS

- Stretching of the lungs during inspiration initiates impulses in afferent pulmonary vagal fibers. These impulses inhibit inspiratory discharge. This is why the **depth of inspiration is increased after vagotomy**.
- When the **CO₂ content of the inspired gas is more than 7%**, the alveolar and arterial PCO₂ begin to rise abruptly in spite of hyperventilation. The resultant accumulation of CO₂ in the body (**hypercapnia**) depresses the central nervous system, including the respiratory centre producing headache, confusion and eventually coma. (**CO₂ narcosis**)
- The point at which breathing can no longer be voluntarily inhibited is called the **breaking point**. Breaking is due to a rise in arterial PCO₂ and the fall in PO₂
- The abrupt increase in ventilation at the start of exercise is presumably due to psychic stimuli and afferent impulses from proprioceptors in muscles, tendons and joints.

- **Cyanosis** is NOT seen in **anemic hypoxia, carbon monoxide poisoning and in histotoxic hypoxia**.
- **Oxygen toxicity** is due to production of **superoxide anion (O₂⁻)**, which is a **free radical** and H₂O₂.

- In febrile patients there is **13% increase in CO₂ production for each degree centigrade rise in temperature**.
- When a normal individual **lies down** the **pulmonary blood volume increases** by up to **400 mL**.

RENAL PHYSIOLOGY

NEPHRON ANATOMY

- There are approximately **1.2 million nephrons** in each kidney.
- The nephron consists of a renal corpuscle, proximal tubule, loop of Henle, distal tubule and collecting duct system.
- The **renal corpuscle** consists of **glomerular capillaries** and **Bowman's capsule**.
- Total **length of nephron** segments (in mm) = **45-65 mm**
 - Proximal tubule, PT = 15 mm
 - Distal tubule, DT = 5 mm
 - Collecting duct, CD = 20 mm
- Differences between the epithelium of the PCT and DCT is given in below table.

PCT	DCT
Abundant microvilli (brush border)	No brush border
Carbonic anhydrase type IV present in luminal membrane	Not present
Has 'leaky' tight junctions	Has 'tight' tight junctions

- **Gap junctions** are present along the lateral cell membrane of PCT, but **not** in DCT
- **Acetazolamide** inhibits both type IV and type II; so it has **primary action on the PCT**.
- PCT has initial **pars convoluta (70% length)** and distal **pars recta**.
- **Loop of Henle (LOH)** is continuation of pars recta of PCT. LOH has 3 parts - thin descending, thin ascending and thick ascending limbs (BUT in **cortical nephron**, **thin ascending part is almost absent**).
- The **connecting tubule** is the segment between distal convoluted tubule and collecting duct. Connecting tubules are unique since they produce and release **kallikrein**.
- The **cuboidal epithelium** of the **collecting ducts** is made up of two types of cells

Principal cells (P cells)	Intercalated (I cells)
Respond to vasopressin - responsible for Na ⁺ reabsorption, K ⁺ secretion and H ₂ O absorption	Alpha cells secrete acid ; beta cells secrete HCO₃⁻
They have few mitochondria and few basolateral infoldings	They have more mitochondria, more microvilli and more basolateral infoldings

- Glomerular capillaries are the **only** capillaries in the body that **drain into arterioles**!
- In humans the **total surface area of the renal capillaries** is equal to the **surface area of tubules**, both being about **12 sq.m**.

Types of Nephron

Cortical nephron	Juxtamedullary nephron
Located in superficial region of cortex	Located in juxtamedullary region
85% of total	15% of total
Shorter LOH	Longer LOH
Thin ascending limb of LOH is absent	Present
Small glomerulus	Large glomerulus
Peritubular capillary network is short	Peritubular capillary forms vasa recta; responsible for counter current exchanger
Blood flow is large (5 ml/gm/min)	Blood flow is less (0.6 ml/gm/min)
pO ₂ is 50 mmHg	pO ₂ is 15 mm Hg
O₂ consumption is high (9 ml/100gm/min)	O ₂ consumption is less (0.4 ml/100gm/min)
O ₂ extraction ratio is very less (0.17)	More (0.83)
Less efficient in concentrating urine	More efficient
More renin content	Less
Mainly involved in urine formation and excretion of waste products	Mainly urine concentration

Renal blood flow numerics

- Renal blood flow = **1260 mL/min** = 25% of cardiac output
- Blood flow** in the **renal cortex is greater** (5 mL/gm/min) than that in the medulla (0.6 mL/gm/min).
- Low blood flow through renal medulla is necessary for maintenance of hyper-osmolar renal medulla.
- Glomerular capillary pressure** is 40% of systemic arterial pressure.
- Renal plasma flow (RPF) = **660 mL/min**.
- Effective renal plasma flow (ERPF) = RPF/PAH clearance = **625 mL/min**.
- Arteriovenous oxygen difference = 14 mL/L. (less than other organs).

EXTRA EDGE

- Measuring renal plasma flow (RPF): – RPF can be estimated using **para-aminohippuric acid (PAH)** because it is both filtered and actively secreted in the proximal tubule. All PAH entering the kidney is excreted.
- PAH clearance** = renal plasma flow.

GLOMERULAR FILTRATION BARRIER

- This is responsible for filtration of plasma according to size and net charge. Composed of
 - Fenestrated capillary endothelium** (size barrier).
 - Fused **basement membrane** with heparan sulfate, collagen, laminin, fibronectin etc (**negatively charged protein barrier**).
 - Inner epithelial layer - **podocytes** - has **foot processes** which interdigitate to form filtration slits bridged by slit diaphragm.
- Slit diaphragm** is made of key proteins called **nephrin (NPHS1)**, **podocin (NPHS2)** etc.... Genetic mutation of these proteins results in glomerular diseases as in below table

Gene	Protein	Disease and Inheritance
NPHS1	Nephrin	Congenital nephrotic syndrome, Finnish type (Phinn1sh!); AR
NPHS2	Podocin	Steroid resistant nephrotic syndrome (SRNS); AR
CD2AP	CD2 associated protein	Adult onset SRNS (FSGS on histology)
ACTN4	Alpha Actinin 4	Adult onset SRNS (FSGS on histology); AD
LAMB2	Laminin Beta 2	Pierson's syndrome; AR
COL4A5,3,4	Collagen IV alpha 5	Alport's syndrome, X-linked

JUXTAGLOMERULAR APPARATUS

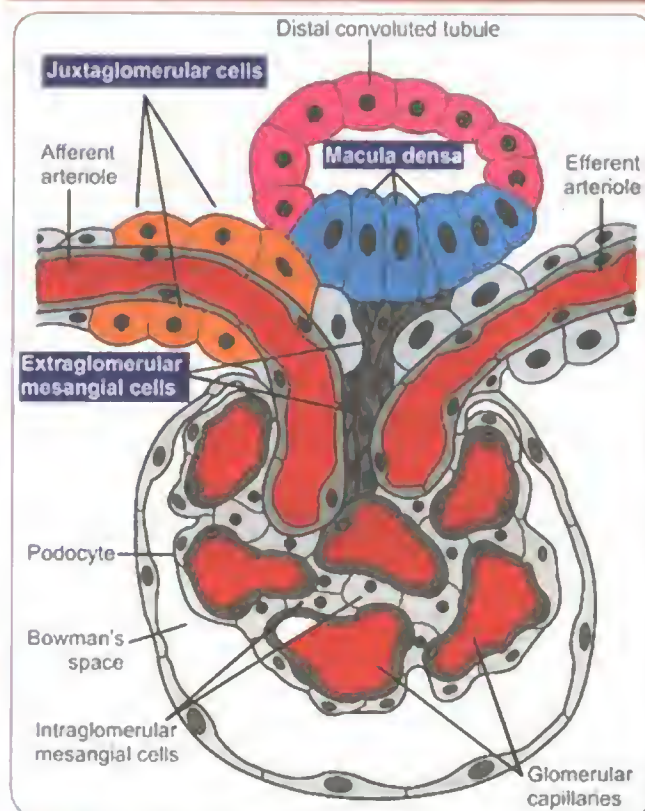


Fig. 3.10: Components of juxtaglomerular apparatus (Highlighted in blue boxes)

Structure	Function
Macula densa - modified epithelial cells of the thick ascending LOH where it comes in contact with the afferent and efferent arterioles	Tubulo-Glomerular feedback: Acts as sensor that monitors the change in ionic composition and rate of flow of tubular fluid - sends feedback signal to renal corpuscle to alter rate of filtration
Juxtaglomerular cells (Polkissen cells) - Modified smooth muscle cells of afferent arteriole with epithelioid appearance	JG cells contain many secretory granules and secrete renin which activates renin angiotensin system involved in regulation of BP
Lacis cells - extra-glomerular mesangial cells	Secrete renin and erythropoietin

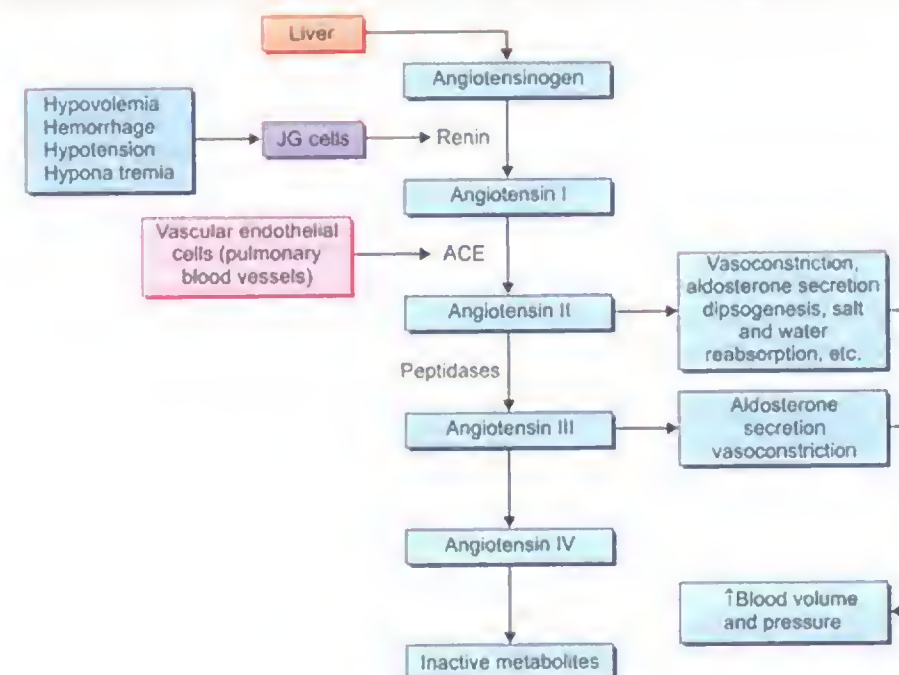
RENIN ANGIOTENSIN SYSTEM

- Renin** is released by the kidneys (juxtaglomerular cells) upon sensing ↓ BP and cleaves **angiotensinogen (from the liver)** to angiotensin I.
- Angiotensin I is then cleaved by **angiotensin converting enzyme (ACE)**, primarily in the lung capillaries to **angiotensin II**.

Actions of angiotensin II:

- Powerful **vasoconstrictor**
- Release of **aldosterone** from adrenal cortex
- Release of **ADH** from posterior pituitary
- Stimulates hypothalamus - ↑ thirst.

Flowchart 3.4: Renin-angiotensin system. (ACE: Angiotensin converting enzyme).



- Overall angiotensin II serves to ↑ **intravascular volume** and ↑ **BP**.
- Atrial natriuretic peptide** released from atria (in response to ↑ atrial pressure) may act as a 'check' on the renin-angiotensin system (e.g. in heart failure). ↓ Renin and ↓ GFR.

GLOMERULAR FILTRATION

Clearance

- Clearance** is the volume of plasma (mL) that would be completely cleared of a substance per minute (per unit time).

- Example for urea clearance is shown below:

$$C_m = U \times V / P$$

where

- C_m = Maximal urea clearance
- U = Urea concentration in urine (mg/mL)
- V = Urine excreted per minute in mL
- P = Urea concentration in plasma (mg/mL).
- Inulin** is a substance that is **neither secreted nor absorbed** in the tubules - **inulin clearance** = glomerular filtration rate (**GFR**).

- Endogenous **creatinine clearance** is used **clinically** to estimate GFR (no longer recommended).

Glomerular filtration rate (GFR)

- Normal GFR** = 125 mL/min or 180 L/day.
- GFR increases** in: exercise; pregnancy; standing for long time; rainy season; males; protein rich diet
- GFR decreases** in: supine position, summer; females; geriatric and children.
- Filtration co-efficient (Kf)** = Glomerular capillary wall permeability × Effective filtration surface area (size of capillary bed)
- $GFR = Kf \times \text{net filtration pressure (NFP)}$

Permeability

- Size of particle:** Neutral substances which are < 4 nm are **freely filtered**; > 8 nm are NOT filtered.
- Charge:** Since glomerular filtration membrane is negatively charged (due to **sialoproteins**); positively charged particles pass through easily.
- Examples of **freely filterable substances** are: Sodium, bicarbonate, glucose, inulin, creatinine, K^+ , Cl^- , myoglobin (partially).

- **Not freely filterable:** Albumin
- **Filtration fraction:** Glomerular Filtration Rate/Renal Plasma Flow i.e., the fraction of RPF filtered across the glomerular capillaries. **Normal filtration fraction = 0.2.**

TUBULAR FUNCTIONS

Proximal Tubule Function

- Proximal tubule is the "**workhorse of the nephron**". It contains **brush border**.
- **Iso-osmotic reabsorption** of 67% (2/3) of the glomerular filtrate occurs here.
- It is site of **active reabsorption** of:
 - 100% of **glucose**: via the Sodium-Glucose Co-transporter - **SGLT1 and SGLT2** (a type of **secondary active transport**). From the tubular cell, glucose is transported into interstitial fluid by **GLUT-2**.
 - 100% of **amino acids** via **SGLT**
 - 65% of **sodium** via Na^+/H^+ exchanger. Other substance that is co-transported with Na^+ is **phosphates**.
 - 90% of HCO_3^- is reabsorbed through Na^+/H^+ exchanger
 - Other substances : **potassium (65%)**, galactose, fructose, amino acids, calcium, uric acid and vitamin C.
- **Passive reabsorption** of
 - 45% of **urea**
 - 65% of **water** (due to the osmotic gradient generated by solute reabsorption) through **aquaporin 1**.
- **Active secretion** of **organic acids** (e.g. PAH, diuretics, salicylates, penicillins and prohenecid) and **ammonia** which acts as a buffer for secreted H^+ .

Loop of Henle Function

- A **counter current multiplier** system exists so that in the presence of ADH, maximum reabsorption of water and concentration of urine takes place.
- **Thin descending loop of Henle:**
 - **Passively reabsorbs water** via medullary hypertonicity (impermeable to sodium). **Makes urine hyper-tonic.**
- **Thick ascending loop of Henle:**
 - **Actively reabsorbs Na^+ , K^+ and Cl^-** ($\text{Na}/\text{K}/\text{Cl}$ cotransporter) and indirectly induces the reabsorption of Mg^{2+} and Ca^{2+} . **Totally impermeable to water**
- **Thus:**
 - Fluid entering loop - isotonic
 - Fluid at tip of loop - hypertonic
 - Fluid leaving loop - hypotonic.

Distal Tubule

- **Actively reabsorbs 7% of Na^+ and Cl^- .**
- **Reabsorption of Ca^{2+}** is under the control of **parathormone**.

Collecting Tubule and Duct

- **ATP driven H^+ proton pump** is mainly responsible for **secretion of H^+** in the distal tubules and collecting ducts - helps to acidify the urine.
- **Reabsorption of water** is regulated by **ADH** (vasopressin).
- Reabsorb Na^+ in exchange for secreting K^+ or H^+ (regulated by aldosterone).

COUNTER-CURRENT SYSTEM

Counter-current multiplier	Counter-current exchange
<ul style="list-style-type: none"> • Formed by thick ascending Loop of Henle and collecting duct • Responsible for production of hyperosmolarity and a gradient in renal medulla • Active process 	<ul style="list-style-type: none"> • Formed by vaso recta • Responsible for maintenance of medullary gradient and hyperosmolarity • Passive process

EXTRA EDGE

- The counter-current system is mainly meant for **concentration of urine**.
- The single most important substance for medullary tonicity is **urea**.
- Counter-current system is **also seen in**
 - **Testis** (pampiniform plexus acts as countercurrent heat exchange system to cool arterial blood before it enters testis)
 - **Intestinal villi:** Oxygen directly diffuses from arterioles to veins.

Transport maximum (T_m)

- **T_m** is the rate at which the tubule maximally transports a particular solute.
- When the concentration of solute in the tubular fluid is more than T_m , the mechanism of transport is said to be **saturated**.
- $T_m = \text{Plasma concentration} \times \text{GFR}$
- T_m for glucose is **375 mg/min** ($300 \text{ mg}/100 \text{ ml} \times 125 \text{ ml/min}$)
- BUT normally glucose appears in the urine (glycosuria) above plasma concentration of **180 mg%** due to **renal spillover**.

BUFFERS IN BLOOD

- **Bicarbonate buffer** ($\text{HCO}_3^-/\text{CO}_2$): 53% of buffering in the body; consists of
 - Plasma HCO_3^- (35%)
 - RBC HCO_3^- (18%)
- Non-bicarbonate buffers (47%); consists of
 - Hb and oxy-Hb (35%)
 - Plasma proteins, organic and inorganic phosphate
- **Most important buffer in human body or plasma (ECF): Bicarbonate**
- **Most important buffer in RBC: Hemoglobin**
- **Most important intracellular buffer (ICF): Protein**
- **MOST abundant buffer in the body = Proteins**, since protein is the major intracellular buffer, and since ICF volume is more than 60% of the total body fluid volume.

EXTRA EDGE

- **Most important** buffer in human body is bicarbonate buffer ($\text{HCO}_3^-/\text{CO}_2$) - **Why??** (AIIMS Nov 2016).
- In buffering by bicarbonate, it is not important to restore HCO_3^- or CO_2 to normal; rather it is **important to restore the $\text{HCO}_3^-/\text{CO}_2$ ratio to normal (i.e. 20)**. The kidneys and the lungs regulate the two elements of this buffer system- CO_2 maybe decreased by hyperventilation and HCO_3^- maybe increased by the kidneys excreting less HCO_3^- .
- Hence the significance of the bicarbonate buffer lies in the fact that the **concentration of both its components can be altered considerably independently of each other**. By alteration in one or the other or both components of the bicarbonate buffer, the extracellular pH can be restored to normal irrespective of the cause of disturbance in pH.

MICTURITION

- A plot of **intravesical pressure against volume of fluid in the bladder** is called a **cystometrogram**.
- The first **urge to void is felt at a bladder volume of 150 mL** and a marked sense of **fullness at about 400 mL**.
- **Law of Laplace** states that the pressure in a spherical viscus is equal to twice the wall tension divided by radius.
- Micturition is mainly a **parasympathetic** activity (S2,3,4).
- **Spastic neurogenic bladder** is seen in **spinal cord injury**.
- After urination the female urethra empties by gravity.
- Urine remaining in the urethra of the male is expelled by several contractions of the **bulbocavernosus muscle**.

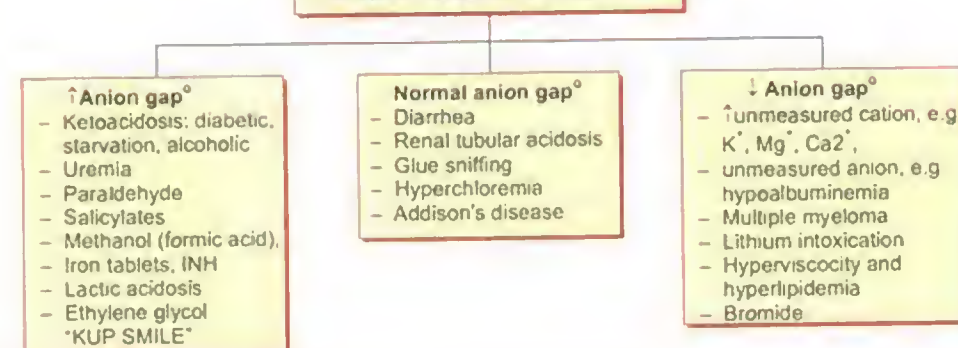
Endocrine function of kidneys

- **Synthesis of erythropoietin** by endothelial cells of peritubular capillaries under stimulus of hypoxia and anaemia.

ANION GAP

- Routine serum electrolyte determination measures most of the cations but only a few anions. This apparent disparity between the total cation and the total anion concentration is called the **anion gap**.
- Anion gap = $[(\text{Na}^+) + (\text{K}^+)] - [(\text{Cl}^-) + (\text{HCO}_3^-)]$ = normally about **10-16 mmol/L**.

Causes of metabolic acidosis with



MORE HIGH YIELD POINTS

- The renal function with which **oxygen consumption** correlates best is the **rate of active transport of sodium**.
- **Dopamine inhibits Na^+/K^+ ATPase** activity in renal tubule cells.

GIT PHYSIOLOGY

GASTROINTESTINAL MOTILITY

Basic Electrical Rhythm

- The smooth muscle of the GIT shows a **spontaneous rhythmic fluctuation** in the **membrane potential** ranging from **-65 mV to -40 mV** - this is called **basic electrical rhythm (BER)** or **gastric slow waves**.
- BER is present in all parts of the GIT **except esophagus**.
- BER is generated by the **pacemaker cells (interstitial cells of Cajal)**
- BER starts in the mid-portion of the stomach near the fundus on the greater curvature of the stomach - **pacemaker of the stomach**.
- BER never causes contraction but coordinates different types of contractions like peristalsis and other 'motor activity' of the GIT.
- BER is **maximum in duodenum - 12/min** and **least in cecum - 2/min**.

Peristalsis

- This is a **reflex response** of GIT to **stretch**, which results in organised propulsion of luminal contents of the gut in forward direction.
- Present in the **entire gut** from esophagus to rectum.
- Stretching of gut wall initiates a circular ring like contraction behind the stimulus (**propulsive segment**) and a relaxation in front of it (**receiving segment**).
- Possible Mechanism of peristalsis: Stretch releases **serotonin** which stimulates the myenteric plexus. From myenteric plexus (1) **retrograde cholinergic neurons** activate neurons that release **substance P and acetylcholine** - these stimulate circular muscle **contraction** (2) **antegrade cholinergic neurons** activate neurons that secrete **VIP and nitric oxide** - these cause **relaxation** of muscle in front of the stimulus.

Deglutitive Inhibition

- A second swallow, initiated while an earlier peristaltic contraction is still progressing in the striated muscle esophagus, causes rapid and complete inhibition of contraction induced by the first swallow. If the first swallow has reached the smooth muscle esophagus, it may proceed distally for a few seconds after the second swallow BUT its peristaltic amplitude diminishes progressively until it disappears.
- Deglutitive inhibition is **secondary to hyperpolarisation of the circular smooth muscle** and is mediated via **nonadrenergic noncholinergic neurons in the myenteric plexus**

- Deglutitive inhibition is **required for drinking liquids which require multiple rapid swallows**—such as **guzzling beer or drinking water/juice fastly**.

Migrating Motor Complexes

- The **migrating motor complex** is a type of cyclic peristaltic contraction occurring in **stomach and small intestine** during the **fasting state** or inter-digestive phase - serves to clear nondigestible food residue from small intestine - hence called **intestinal housekeeper!**.
- It is different from regular peristalsis since a large portion (20-30 cms) of stomach/intestine is involved in the contraction.
- Velocity** of MMC = **5 cm/min**; velocity **decreases from duodenum to ileum**.
- MMC occurs once in every **90 minutes**.
- MMC is **abolished immediately after entry of food** in the stomach.
- MMC is **vagally mediated** but **matlln may also stimulate** the MMC.
- Three phases of MMC are:
 - Phase 1**: Period of **quiescence** with no spikes or contractions
 - Phase 2**: **Intermittent** pressure activity
 - Phase 3**: **Activity front**; a series of high amplitude rapid spikes corresponding to strong rhythmic gut contractions

Segmentation

- This commonly occurs in **small intestine** and is characterized by closely spaced contraction of circular muscle layer.
- These contractions divide the small intestine into many segments - hence called **segmentation**.
- It's main purpose is the mix chyme with pancreatic and intestinal secretions - hence also called '**mixing movements**'.

Types of Gastric Motility

- Hunger contractions**: Occurs when stomach is empty for long duration; they are painful.
- Receptive relaxation**: Relaxation of fundus and body of stomach in response to chewing and swallowing of food; occurs due to **VIP and nitric oxide**.
- Adaptive relaxation**: Relaxation of stomach triggered by distension of stomach, mediated by **vasovagal reflex**.
- Feedback relaxation**: reflexive relaxation that occur due to presence of food in proximal segment of small intestine.
- Peristalsis, Migrating motor complex and reverse peristalsis**.

Factors Regulating Gastric Emptying

Stimulate emptying/ faster emptying

Liquid foods
Carbohydrates and proteins
Gastrin
Vagal stimulation

Inhibit emptying/slower emptying

Solid foods
Fats
CCK, secretin, GIP
Acid in duodenum

EXTRA EDGE

- As **fat decreases gastric emptying**, a cup of fat/cheese taken before alcohol ingestion (at parties) ensures slower gastric emptying and slower absorption of alcohol from the intestine!

GASTROINTESTINAL HORMONES

Hormone and source	Regulation	Actions	Remarks
Gastrin G cells in gastric antrum . Gastrin producing cells also present in vagus and sciatic nerve; hypothalamus, anterior pituitary, medulla and fetal pancreas	↑ gastrin release by: <ul style="list-style-type: none"> Peptides (most potent) and amino acids (phenylalanine and tryptophan) Stomach distension Vagal stimulation via GRP Epinephrine Calcium ↓ gastrin release by: <ul style="list-style-type: none"> Acid in stomach (pH < 1.5) somatostatin secretin, VIP, GIP, calcitonin and glucagon 	↑ gastric acid (H⁺) secretion (main action). ↑ pepsin and intrinsic factor secretion ↑ gastric motility and emptying ↑ growth of gastric mucosa ↑ insulin secretion	Hypergastrinemia occurs in Zollinger Ellison syn. (gastrinoma - non-β cell tumors of pancreas) and pernicious anemia . 3 types of physiologically important gastrin are G17 (main type) and G34 and G14 Gastrin is polypeptide hormone exhibiting macro-heterogenicity (gastrins having different polypeptide lengths) and micro-heterogenicity (gastrins having different molecular structure)
Cholecystokinin (CCK) I cells of proximal 2/3 of small intestine (duodenum and jejunum)	↑ CCK release by: <ul style="list-style-type: none"> Fatty acids (but NOT triglycerides) Amino acids Peptides Cations e.g. Ca²⁺ and Mg²⁺ Bile and pancreatic juice NOT carbohydrates 	↑ gallbladder contraction (and relaxation of sphincter of Oddi) for bile secretion ↑ pancreatic enzyme and bicarbonate secretion ↑ growth of exocrine pancreas ↑ motility of small intestine and colon ↓ gastric emptying ↓ gastric acid secretion Augments secretin actions to produce alkaline pancreatic secretion	In cholelithiasis pain worsens after fatty food ingestion due to ↑ CCK . Half life of CCK is 5 minutes . Since CCK increases pancreatic enzymes it is also called CCK-PZ. CCK- pancreozymin!
Secretin S cells of proximal 2/3 of small intestine (duodenum and jejunum)	↑ by acid H⁺ (most potent stimulus) and products of protein digestion (vagus has NO direct action on secretin secretion)	↑ pancreatic HCO₃⁻ secretion ↑ alkaline bile secretion ↓ gastric acid and pepsin secretion Contracts pyloric sphincter	↑ HCO₃⁻ neutralizes gastric acid in duodenum allowing pancreatic enzymes to function. Secretin was first hormone to be discovered by Bayliss and Starling in 1902.
Gastric inhibitory peptide (GIP) K cells of duodenum and jejunum	↑ by glucose, fatty acids and amino acids (only GI hormone stimulated by all 3 types of food)	↑ postprandial insulin secretion (main action) ↓ gastric H⁺ secretion	Level of insulin in response to GIP resembles the concentration of insulin attained following oral glucose ingestion - hence GIP is also called Glucose-like Insulinotropic Peptide Oral glucose is better at triggering release of GIP than IV glucose

Contd..

Contd..

Hormone and source	Regulation	Actions	Remarks
Vasoactive intestinal peptide (VIP) From mucosal cells of GIT from stomach to colon, BUT more in colon; Also found in nerves of GIT and other autonomic nerves, blood and brain	↑ by distension and vagal stimulation ↓ by adrenergic input	↑ pancreatic and intestinal secretion rich in electrolytes and water (hence watery diarrhea) It causes vasodilation (leads to hypotension) ↑ relaxation of GI smooth muscle including lower esophageal sphincter ↓ gastric acid, H ⁺	VIPoma – non-α, non-β, Islet cell pancreatic tumor that secretes VIP: Abundant diarrhea and hypotension.
Motilin By enterochromaffin cells and Mo cells in mucosa of all parts of GIT except esophagus and rectum	↑ in fasting states	↑ gastric and intestinal motility (major cause of migrating motor complexes)	Erythromycin binds to motilin receptors in the gut and increases intestinal motility
Somatostatin Throughout GI mucosa; hypothalamus and D cells of pancreas	↑ by acid ↓ by vagal stimulation	↓ gastric acid, H ⁺ ↓ release of all GI hormones ↓ gall bladder contraction	Inhibitory hormone; Anti-growth hormone effects (digestion and absorption of substances needed for growth); Used to treat VIPoma and carcinoid tumors

EXTRA EDGE

- **Peptide YY** is responsible for "**ileal brake**" phenomenon.

- **Substance P** increases intestinal motility.

Must Know points about GI juices

- Most **alkaline fluid is pancreatic** juice and most **acidic is gastric** juice.
- **Maximum K⁺** secreted per day is in saliva.
- **Maximum Na⁺** concentration is in bile.
- **Maximum Cl⁻** concentration is seen in gastric juice > bile.

SALIVARY SECRETION

- About **1.5 L** of saliva is secreted per day.
- Salivary **pH = 7 (alkaline)**.
- Saliva contains mainly **water (99.5%)** and some solids (0.5%).
- **High K⁺ and HCO₃⁻**, low Na⁺ and Cl⁻.
- Composition **varies with flow rate**
- Low flow rate = hypotonic; High flow rate = **Isotonic** (closer to plasma); overall in humans, **saliva is always hypotonic to plasma** (tonicity is **70%** that of plasma).
- **Ptyalin (α-Amylase)** begins initial starch digestion; inactivated by low pH on reaching stomach.
- **Lingual lipase** helps in **triglyceride digestion**
- **Mucins** (glycoproteins) **lubricate food**.
- **Bicarbonates** neutralize oral bacterial acids, maintains dental health.

Glucagon-like Peptide (GLP)

- Glucagon is produced from A cells in pancreas and L cells in intestine.
- In L cells, glucagon is processed to form glicentin and glucagon-like peptides (GLP).
- GLP1 and GLP2 are also produced in the brain.
- GLP-1 is a potent stimulator of insulin secretion.

Salient Features of Other GI Hormones

- **Neurotensin**: **Inhibits GI motility** and increases ileal blood flow.
- **GRP**: Gastrin releasing polypeptide secreted from **non-cholinergic vagal fibres**; it mediates gastrin release via no-cholinergic stimulation; it is similar to bombesin of amphibians.
- **Guanylin**: Secreted by **Paneth cells** in the crypts of Lieberkuhn of small intestine; it stimulates **guanylyl cyclase** which increases **cGMP** - in turn leads to increased chloride secretion into intestine. Some strains of E.coli activate guanylin receptors and cause diarrhea.
- **Ghrelin**: Strong **orexigenic (appetite stimulating)** agent.

GASTRIC SECRETION**Gastric Cell Types**

Chief (peptic or zymogen) cells	MC cells Occur in body and fundus They are present in the basal part of the glands Secrete pepsinogen
Oxyntic (parietal cells)	Occur only in the body : most numerous in the upper half of the gland on the side walls and near duct of the gland; They secrete HCl and Intrinsic factor
G-cells	Occur in gastric antrum ; secrete Gastrin .
Other cells	Mucus neck cells, argentaffin cells, undifferentiated columnar cells.

Phases of Gastric Secretion

Phase	Stimuli and Regulation
Cephalic	Chewing, swallowing (before food enters the stomach) Mediated by vagus nerve (para-sympathetic) Accounts for 30-50% of gastric juice secretion
Gastric	Distension of stomach stimulates Local vasovagal reflex Digested proteins stimulate Gastrin, Histamine Accounts for 50-60% of gastric juice secretion
Intestinal	Products of digestion and acidic chyme activates various intestinal reflexes

PANCREATIC SECRETION

- **Composition**: Similar Na⁺ and K⁺ as plasma, isotonic.
- **Amylase** – starch digestion, secreted in active form
- **Lipase, phospholipase, colipase** – fat digestion
- **Proteases** (trypsin, chymotrypsin, elastase, carboxypeptidases) – protein digestion, secreted as proenzymes also known as '**zymogens**'.
- Trypsinogen is converted to trypsin by enterokinase secreted from duodenal mucosa. Trypsin activates other proenzymes and more trypsinogen forms (**positive feedback**).
- **Cystic fibrosis**: Defect in **Cl⁻ channels** due to mutation in **CFTR gene on chromosome 7**; a/w deficient pancreatic enzymes resulting in **malabsorption** and **steatorrhea**.

ABSORPTION OF NUTRIENTS IN THE GUT**Absorption of Carbohydrates**

- Only **monosaccharides** (glucose, galactose, fructose) are absorbed by enterocytes.
- **Glucose and galactose** are taken up via Na⁺ dependent **SGLT1**.
- Fructose is taken up exclusively by Facilitated diffusion by **GLUT-5**. This process is **Na⁺ independent**.

Sites of absorption

- **Iron**: Duodenum and Proximal jejunum
- **Calcium, folate**: Jejunum
- **Vitamin B₁₂** and bile salts: Terminal ileum
- Carbohydrates, proteins and lipids - **duodenum**

CNS SENSORY PHYSIOLOGY**MYELIN**

- Some aspects of myelination have been dealt with already under nerve physiology. Some more points here.
- Myelination occurs **centrifugally** i.e. **first peripheral nerve** and then spinal cord (dorsal column), brainstem, cerebellum, basal ganglia, thalamus and **lastly cortex** is myelinated.
- **Sciatic nerve** is myelinated at **12 weeks** of gestation (**earliest**).
- Nerve is myelinated in **proxim-distal** manner, along the growth of the peripheral nerve.
- **CNS myelination** evident at **24 weeks** of gestation.

- **Corpus callosum** starts myelination at **8 weeks after birth**.
- The **last area to myelinate** is the **subcortical area of frontal and temporal lobe** (myelinate near adulthood).

SENSORY RECEPTORS**Based on Function**

- **Exteroceptors**: are present in the **skin and subcutaneous tissues** and provide information about **change in external environment close to the body** (touch, pressure, temperature etc.)
- **Proprioceptors**: Provide information about the **position of the body** in space; they are mechanoreceptors

present in the muscles, tendons and joints. These include muscle **spindles**, **Golgi tendon organs** and **joint-capsule receptors**.

- **Interoceptors:** Detect changes in the internal environment of the body ex **baroreceptors** sensing BP changes; **chemoreceptors**, **osmoreceptors** etc.
- **Teleceptors:** Receptors that *receive stimuli or sensation that are present far away from the body*- ex: **auditory receptors** detect sound coming from a distance.

Based on Manner in which Stimulated

- **Mechanoreceptors:** Respond to application of **mechanical stimulus**. Three types are
 - **Expanded endings:** Merkel's discs and Ruffini endings
 - **Encapsulated endings:** Pacinian corpuscles; Meissner's corpuscles and Krause end bulbs
 - **Naked nerve endings** (free nerve endings)
- **Thermoreceptors**
- **Cold receptors:** Sensitive between 10-40 deg C
- **Warmth receptors:** Sensitive between 30-49 deg C
- **Nociceptors:** Respond to painful stimuli.
 - **A-delta** mechanical nociceptors: Respond to **fast pain** (sharp prick)
 - **C-polymodal** nociceptors: Respond to **thermal and chemical** stimuli.

EXTRA EDGE

- Actually, nociceptors are ion channels, which are called **Transient receptor Potential (TRP)** channels
- Receptor for **moderate cold: CMR-1** (cold and methanol sensitive receptor)
- Receptor for **noxious/painful heat: Vanilloid** receptors

Tactile Receptors

- Tactile receptors are **mechanoreceptors** and are of two types
- **Rapidly adapting (phasic) receptor:**
 - Detect **flutter and vibration**.
 - Adapt **within 1/10th** of a second
 - Trigger nerve impulse only when stimulus is applied.
 - For example **Pacinian corpuscle**, **Meissner's corpuscle**, **hair end organ**
- **Slow adapting (tonic) receptor:**
 - **Continue to trigger nerve impulses** for as long as the stimulus persists.
 - Adaptation that takes **1 second or longer** is slow adaptation

- Detect **sustained pressure** and object **form** (shape, size, texture), e.x. **Merkel cells**, **Ruffini endings**, **free nerve endings**, **baroreceptors**, **pain receptors**

Receptor	Location	Comments
Pacinian corpuscle	Dermis	Senses vibration . Most sensitive mechanoreceptor in the sensory system.
Meissner's corpuscle	Dermal papillae of glabrous (hairless) skin	Senses lateral motion (movement). Constitutes 40% of fingertip receptors (it is the most numerous receptor in the hand)
Merkel cell	Tip of epidermis	A.k.a iggodome receptor. Senses static touch (shape, edges, corners, textures). Responsible for reading Braille in blind persons
Ruffini ending	Dermis	Senses skin stretch .

Muscle Spindles

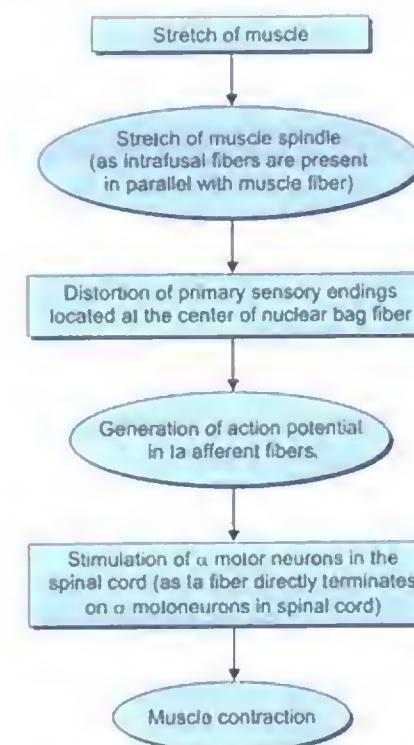
- **Stretch receptors** within a muscle are called **muscle spindles** - present in all **skeletal muscles**.
- Muscle spindle **density is higher** in muscles a/w **fine movements** - eye muscles and lumbricals.
- Muscle fibres within the spindle are called **intrafusal** fibers to differentiate them from the regular or **extrafusal** fibers (contractile units of muscle).
- Intrafusal fibers are **parallel** to extrafusal fibres BUT they do NOT have any contractile function.
- The two types of intrafusal fibres are:
 1. **Nuclear Bag fibres:** they have bulge in the centre containing many nuclei. Usually there are **two** nuclear bag fibres **per spindle** - nuclear bag fiber 1 has **low** myosin ATPase activity and nuclear bag fiber 2 has **high** myosin ATPase activity.
 2. **Nuclear chain fibers:** **Thinner and shorter**; usually **4 or more** are present per spindle.
- The **central noncontractile** part of muscle spindle contains the receptors whereas **peripheral part contains contractile** elements.
- Two types of sensory nerve fibres (afferent) originate from intrafusal fibers:
 1. **Aunulospiral (primary):** 1 in number; wraps around the centre of the nuclear bag and nuclear chain fibers. These are **A-alpha** or **1a** fibres. They have both static and dynamic response
 2. **Flower-spray (secondary)** endings: Innervate the peripheral parts (ends) of nuclear bag and nuclear

chain fibres. Do NOT innervate dynamic nuclear bag fibres.

- Motor (efferent) innervation of muscle spindle:
 - Gamma-motor neurons innervate nuclear bag fibers- also called efferents of Lékell. They increase the sensitivity of the muscle spindle to stretch.

- Muscle spindles are the main component of the **stretch reflex (myotactic reflex)**. Stimulus for stretch reflex is **passive stretch**.
- Various other factors that increase gamma motor neuron discharge are: **Stimulation of skin** (by noxious agents); **Jendrassik maneuver**; **anxiety** and **unexpected movement**.

Flowchart 3.5: Mechanism of muscle contraction in response to muscle stretch



Golgi Tendon Organ

- Golgi Tendon organ (**GTO**) is embedded within the **muscle tendon**.
- GTO consists of net-like (ramified) collection of **knobby nerve endings**. There are **3-25 muscle fibers** per Golgi tendon organ.
- Unlike the **muscle spindle** which acts a **length detector** (length feedback), **GTO** acts as a **muscle tension detector** (force feedback).
- GTO are formed by terminals of group **1b afferent** fibres - these fibers terminate on **inhibitory interneuron**. So activation of golgi Tendon reflex results in **relaxation of muscle** - **inverse stretch reflex**.
- Thus Golgi Tendon reflex is a **protective reflex** that **prevents excessive rise in muscle tension**.

- **Stimulus** for Golgi Tendon reflex is **active contraction** of muscle >> passive stretch.

	Stretch reflex	Golgi tendon reflex
Type	Monosynaptic , no interneuron	Bisynaptic , inhibitory interneuron involved
Stimulus	Passive muscle stretch	active contraction of muscle >> passive stretch
Response	Muscle contraction	Muscle relaxation
Afferent fiber	1a	1b
Detects	Muscle length	Muscle tension
Receptor	Muscle spindle parallel to muscle fiber	GTO in series with muscle fiber

Flexor- withdrawal reflex

- Typical **polysynaptic reflex** occurring in response to **painful** stimulation (group III, IV fibers) and **touch** (group II fibers).
- Group II, III and IV are known as **flexor reflex afferents**.
- Components of withdrawal reflex are:
 - **Flexor** reflex (ipsilateral flexion)
 - **Reciprocal** inhibition
 - **Crossed extensor** response (contralateral extension)
 - After discharge (lasting for many seconds after stimulus is over).

EXTRA EDGE

- **Spasticity**: Excessive discharge to **gamma motor neuron**. Excessive time in one group of muscles (extensors), e.g. clasp knife reflex or lengthening reaction - an exaggerated form of Golgi tendon reflex.
- **Rigidity**: Increased activity of **alpha motor neurons** to both agonist and antagonist muscles. Ex: Lead pipe rigidity, cogwheel rigidity - seen in extrapyramidal disease.
- **Clonus**: Repetitive muscular contraction in response to stretch due to operation of **stretch and inverse stretch** reflex.

NEUROTRANSMITTERS

Neurotransmitter	Physiologic anatomy	Clinical aspects
Acetylcholine Excitatory: Nicotinic Inhibitory: Muscarinic	Motor neurons in spinal cord → neuromuscular junction . Basal forebrain → widespread cortex Interneurons in striatum Autonomic nervous system: Preganglionic sympathetic . Preganglionic and Postganglionic parasympathetic Also some postganglionic sympathetic to sweat glands and postganglionic sympathetic vasodilator fibres to blood vessels in some skeletal muscles. Cortex (Betz cell)	Acetylcholinesterases (nerve gases) Myasthenia gravis (antibodies to ACh receptor) Congenital myasthenic syn. (mutations in ACh receptor subunits) Lambert-Eaton syndrome (antibodies to Ca channels impairs ACh release) Botulism toxin (disrupts ACh release by exocytosis) Alzheimer's disease (selective cell death) AD frontal lobe epilepsy (mutations in CNS ACh receptor) Parkinson's disease (tremor)
Dopamine	Substantia nigra → striatum (nigrostriatal pathway) Substantia nigra → limbic system and widespread cortex Arcuate nucleus of hypothalamus → anterior pituitary (via portal veins)	Parkinson's disease (selective cell death) MPTP parkinsonism (toxin transported into neurons) Addiction, behavioral disorders Inhibits prolactin secretion
Norepinephrine (NE)	Locus coeruleus (pons) → limbic system, hypothalamus, cortex Medulla → locus coeruleus, spinal cord Postganglionic sympathetic neurons	Mood disorders (MAO inhibitors and tricyclics increase NE and improve depression) Anxiety Orthostatic tachycardia syndrome (mutations in NE transporter)
Serotonin	Pontine raphe nuclei → widespread projections Medulla/pons → dorsal horn of spinal cord	Mood disorders (SSRIs improve depression) Migraine pain pathway Pain pathway
γ-Amino Butyric Acid (GABA)	Major inhibitory neurotransmitter in brain; Widespread cortical interneurons and long projection pathways	Stiff person syndrome (antibodies to glutamic acid decarboxylase, the biosynthetic enzyme for GABA) Epilepsy (gabapentin and valproic acid increase GABA)
Glycine	Major inhibitory neurotransmitter in spinal cord	Spasticity Hyperekplexia (myoclonic startle syndrome) due to mutations in glycine receptor
Glutamate	Major excitatory neurotransmitter; located throughout CNS, including cortical pyramidal cells	Seizures due to ingestion of domoic acid (a glutamate analogue) Rasmussen's encephalitis (antibody against glutamate receptor 3) Excitotoxic cell death

SOMATOSENSORY PATHWAYS

Tract and location	1st order neuron	2nd order neuron	Function
Dorsal tract; Posterior spinal cord	Sensory nerve ending in periphery → enters Cell body in dorsal root ganglion → enters Spinal cord and ascends in fasciculus gracilis and cuneatus (dorsal column) to synapse in Nucleus gracilis and cuneatus in medulla	Decussates in medulla → ascends Contralaterally in medial lemniscus → 2 nd synapse in VPL of thalamus → reaches sensory cortex (3 rd order neuron)	Ascending pressure, vibration, fine touch, proprioception, two-point discrimination .
Spinothalamic tract; Anterior spinal cord	Sensory nerve ending in periphery (A-δ and C fibres) → enters cell body in dorsal root ganglion → enters spinal cord and synapses in the dorsolateral tract of Lissauer (in ipsilateral gray matter of spinal cord)	Decussates at anterior white commissure → ascends contralaterally in lateral spinothalamic tract → 2 nd synapse in VPL of thalamus → reaches sensory cortex (3 rd order neuron)	Anterior spinothalamic tract: Crude touch and pressure (less role) Lateral Spinothalamic Tract: Ascending pain and temperature sensation. ("Thando Gorum = sPain-O-Thalam! (tract)!!!".

EXTRA EDGE

- **Dorsal column** organization: Fasciculus gracilis = **Legs**; cuneatus = **arms**; i.e., *just as in normal humans, arms outside and legs inside*.
- **Unconscious proprioception** travels in nucleus dorsalis (**Clarke's column**) through **anterior and posterior spinocerebellar** tract.

LAWS IN SENSORY PHYSIOLOGY

Muller's doctrine of specific nerve energies

- When the nerve pathways from a particular sense organ are stimulated, the sensation evoked is that for which the **receptor is specialized** no matter how or where along the pathway the activity is initiated.

Law of projection

- No matter where along the sensory nerve pathway (along its course to the cortex), one stimulates, the conscious sensation produced is **referred to the location of the receptor**. e.g. in **phantom limb**.

Weber-Fechner law

- The magnitude of the sensation felt is proportional to the log of the **intensity** of the stimulus (intensity discrimination)

Bell-Magendie law

- This states that the **Dorsal** root is **Sensory** and **Ventral** root is **Motor**. ("Doctors Study Very Much!")

Labelled line theory

- All the sensations from different parts of the body travel along specified paths (ex: posterior column, fibers from the lower parts of the body are placed medially)

CNS MOTOR PHYSIOLOGY

Pyramidal Tracts

- **Pyramidal tract** = **corticospinal tract**.
- Pyramidal tract pathway: The UMN originates in **layer V** of cerebral cortex (internal capsule and midbrain) > **decussates** at level of medullary **pyramids** (80% fibers) > descends contralaterally in the corticospinal tracts > synapse in the anterior horn of the spinal cord > LMN leaves spinal cord through the anterior horn > reaches the neuromuscular junction.

- **20% fibers** that do not decussate in the medulla and pass ipsilaterally form the **anterior (ventral) corticospinal tract**.

Extrapyramidal Tracts

- **Extrapyramidal tract** = all descending tracts other than corticospinal tract - these **do NOT** pass through the pyramid in the medulla - include
 - Basal ganglia
 - Rubrospinal tract
 - Tectospinal tract
 - Vestibulospinal tract
 - Reticulospinal tracts.

Organization of Descending Tracts in Spinal Cord

Tracts in Lateral white matter	Tracts in anterior white matter
<ul style="list-style-type: none">• Lateral corticospinal tract• Rubrospinal tract• Medullary corticospinal tract	<ul style="list-style-type: none">• Vestibulospinal tract• Tectospinal tract• Anterior corticospinal tract• Pontine reticulospinal tract

Contd...

Contd...

Tracts in Lateral white matter	Tracts in anterior white matter
Involved in regulation of skilled voluntary movements as lateral group of motor neurons Innervate the distal limb muscles	Involved in regulation of posture as medial group motor neurons innervate the proximal limb muscles and muscles of axial skeleton

UMN vs LMN Lesions

	UMN lesions	LMN lesions
Anatomy	The corticospinal tract path extending from the brain down to but not including the anterior horn cells of the spinal cord ('CNS lesions')	Extending from the anterior horn cells of the spinal cord to the peripheral nerve ('PNS lesions')
Paresis	Affects upper extremity extensors more than flexors, and the lower extremity flexors more than extensors	Distribution of motor neurons, dermatome and root. Affects the trunk, cord or nerves
Tone	↑, Spasticity	↓ Flaccidity
Deep tendon reflexes		↓ or absent
Plantar reflexes	Upgoing (+ extensor Babinski's)	Downgoing (normal)
Wasting/Atrophy	Absent	Present
Fasciculations	Absent	Present
Examples	Lesions in the cerebrum, basal ganglia, brainstem, cerebellum or spinal cord: strokes, TIA, brain tumors, head trauma, AIDS, MS	Guillain Barre syn., neuropathies, myopathies, myasthenia gravis, Bell's palsy, herpes zoster
Mnemonic	"Upper MN = everything Up (tone, DTR, toes)"	"Lower MN = everything lowered/down (tone, DTR, downgoing toes, less muscle mass)"

Spinal Shock

- **Transection of the spinal cord** is immediately followed by a period of **spinal shock** during which all spinal reflexes are **profoundly depressed**.
- Return of reflexes (which are hyperactive) occurs due to **denervation hypersensitivity**.
- **Earliest reflex to reappear** is **bulbocavernosus** reflex.
- Flexor reflex to noxious stimulus (**flexor withdrawal reflex**) reappears before **deep tendon reflex** (stretch reflex).

- **Righting reflexes** are **absent** and animal lies on the ground.
- **Tonic reflexes** are prominently **marked**.
- The **reticulospinal tract** (via **gamma** motor neurons) is the **principal regulator of muscle tone** along with **vestibulospinal tract** (via **alpha** motor neurons).
- **Excessive discharge of gamma motor neurons** leads to decerebrate rigidity (a misnomer since this is actually a type of spasticity!).
- Decerebrate posturing indicates **M2** on Glasgow coma scale.

Decerebrate Rigidity

- Decerebrate rigidity is produced in animals by causing a **midcollicular section of the brainstem** (at upper border of midbrain between the superior and inferior colliculi).
- Features of decerebrate preparation are:
 - **NO** phenomenon similar to spinal shock is produced.
 - **Severe spasticity** is immediately observed in the **extensor antigravity muscles** (extensor of lower limbs in humans).

Decorticate Rigidity

- Decorticate rigidity is produced by **removing the whole cerebral cortex** but leaving the basal ganglia intact.
- Features of decorticate animal are:
 - **NO** features of shock.
 - All midbrain reflex activities are **intact**.
 - **Rigidity/hypertonia** is **very minimal** and present only at rest.

- **Hopping and placing reactions** are severely impaired.
- Striking defect is **inability to react in terms of past experience**.
- **Temperature regulation is intact**
- **Visceral homeostatic mechanisms** are intact.
- **Flexion of upper limbs and extension of lower limbs**.
- Decorticate posturing indicates **M3** on Glasgow coma scale

POSTURAL REFLEXES

- **Stretch reflex** is fundamental to posture control.
- Righting reflexes are a type of postural reflexes responsible for our apparently effortless ability to stay 'right side up'; they do not require 'thought' to be initiated.
- Important postural reflexes and their integrating centers are given below

Postural reflex	Integrating centre
Stretch reflex	Spinal cord
Positive supporting reaction (Magnet)	
Crossed extensor reflex	
Tonic labyrinthine reflex	Medulla
Tonic neck reflex	
Righting reflex (labyrinthine RR, neck RR, body RR, limb RR)	Midbrain
Grasp reflex Vestibular placing reaction	
Optical righting reflex	Cortex
Conditioned reflex	
Hopping and Placing reaction	

EXTRA EDGE

- **Sham rage**: When connection between cerebral cortex and hypothalamus is removed by **decortication**, the experimental animal exhibits outburst of rage on mild peripheral stimulation. This is called "**shom rage**" since the emotions associated with rage are absent. This **shom rage is due to release of hypothalamus** from cortical control and it can be abolished by lesioning the caudal hypothalamus.

PHYSIOLOGY OF LOBES OF THE BRAIN

Functions of Lobes of the Brain

Lobe	Function
Frontal	Personality, emotional control, social behavior, contralateral motor control, language, micturition
Parietal: dominant	Language, calculation
Parietal: nondominant	Spatial orientation, constructional skills
Temporal: dominant	Language, auditory perception, verbal memory, smell, balance
Temporal: nondominant	Auditory perception, melody/pitch perception, non verbal memory, smell, balance
Occipital	Visual processing

Features of Localized Cerebral Lesions

Frontal lobe	<ul style="list-style-type: none">• Hemiparesis; fits (contralateral movement)• Personality changes (indecent, indolent, indiscreet, <i>disinhibition</i>)• Positive primitive reflexes (<i>grasp reflex</i>) - significant only if unilateral• Dysphosia (Broca's area)• Loss of smell unilaterally.
Temporal lobe	<ul style="list-style-type: none">• Hallucinations (smell, taste, sound, <i>déjà-vu</i>)• Complex partial seizures with automatism; Dysphosia• Field defect (contralateral superior quadrantanopia, 'pie in the sky');• Forgetfulness; Functional psychosis: Fear/rage; Hypersexuality.
Parietal lobe	<ul style="list-style-type: none">• Hemisensory loss• ↓ 2-point discrimination• Astereognosis (↓ ability to recognize object held in hand by touch alone);• Field defect (contralateral inferior quadrantanopia, 'pie on the floor');

Contd...

Contd...

- **Sensory inattention**; dysphasia
- **Gerstmann's syndrome** (finger agnosia, right/left disorientation, dysgraphia and acalculia = **dominant parietal lesion**)
- **Hemispatial neglect** (ignoring one side of body), trouble with *dressing* (nondominant parietal lobe lesion)
- **Balint's syndrome**: Involves deficits in the orderly visuomotor scanning of the environment (**Oculomotor apraxia**) and in accurate manual reaching towards visual targets (**Optic ataxia**), and an inability to integrate visual information in the center of gaze with more peripheral information (**Simultanagnosia**) - overall spatial disorientation due to lesion of network for spatial attention.
- **Occipital lobe**
- **Cerebellum**
- **Cerebellopontine angle**
- **Carpus Callosum (rare site for lesions)**
- **Midbrain**

Language Disturbance

- The **left hemisphere is dominant** (i.e., controls language) in 99% of right handed and 60% of left handed people

Type of aphasia	Features	Comments
Broca's (expressive/motor) aphasia	Nonfluent speech, good comprehension; poor repetition and naming	Occurs due to superior division MCA stroke ; site of lesion is posterior part of inferior frontal gyrus (Broca's area 44,45) (" BRO ca's = BRO ken speech")
Wernicke's (receptive, sensory) aphasia	Fluent speech; poor comprehension, repetition and naming ; neologisms/paraphasias are common	Occurs due to inferior division MCA stroke ; site of lesion is posterior third of superior temporal gyrus (Wernicke's area 22) (" W ernicke's = full of Words , but makes no sense! ")
Conduction aphasia	Fluent speech and good comprehension; poor repetition	Lesions of arcuate fasciculus which connects Wernicke's to Broca's area; due to embolic stroke in the posterior temporal branch of MCA
Anomic aphasia	Fluent speech, comprehension and repetition; inability to remember names of things, people or places	MC language disturbance seen in head trauma and metabolic encephalopathy , also MC aphasia seen in Alzheimer's disease

COMPARISON OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM

Feature	Sympathetic	Parasympathetic
Location of preganglionic neuron	Thoracolumbar segments of spinal cord	Nuclei of III, VII, IX and X cranial nerves and sacral (S2-S4) segments of spinal cord
Location of postganglionic neuron	Away from target organ	Near or in the target organ
Length of preganglionic fiber	Relatively short	Relatively long
Length of postganglionic fiber	Relatively long	Relatively short

Contd...

Contd. .

Feature	Sympathetic	Parasympathetic
Preganglionic neurotransmitter	Acetylcholine	Acetylcholine
Postganglionic neurotransmitter	Noradrenaline	Acetylcholine

MOVEMENT DISORDERS

- **Chorea** = dance (Greek); **Sudden, jerky, purposeless movements**; characteristic of **basal ganglia lesions**.
- **Athetosis** = not fixed (Greek); **Slow, writhing movements**, especially of fingers
- **Hemiballismus** = **Sudden, wild flailing of one arm**; characteristic of **contralateral subthalamic nucleus**

Levon; loss of inhibition of thalamus through globus pallidus

Tremors

- **Resting (static) tremor**: In **Parkinson's disease** (pill rolling tremor)
- **Intentional tremor**: In **cerebellar** lesion
- **Postural tremor**: In **thyrotoxicosis**, essential familial tremor
- **Flapping tremor/asterixis**: In **hepatic encephalopathy**, renal failure, resp. failure, metabolic encephalopathy
- **Perilar tremor**: General paresis of insane
- **Holmes tremor**: **Mibrain or rubral tremor**; caused by lesion close to **red nucleus**.
- **Pill rolling tremor**: Parkinsonism

PERIPHERAL NERVE REFLEXES "JERKS"

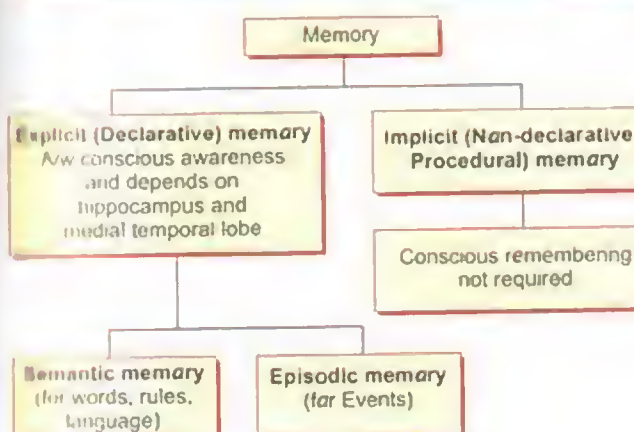
- Deep tendon reflexes are classic examples of **monosynaptic stretch reflex (myotatic reflex)**.

Reflex	Root value
Biceps jerk	C5, C6
Supinator jerk (Brachioradialis)	C5, C6
Triceps jerk	C7, C8
Finger jerk	C8
Knee jerk (patellar or quadriceps)	L3, L4
Ankle jerk (Achilles)	S1, S2

EXTRA EDGE

- Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (**Jendrassik maneuver**), e.g. upper limb reflexes may be reinforced by voluntary teeth-clenching, and the Achilles reflex by hooking the flexed fingers of the two hands together and attempting to pull them apart.

MEMORY



- **Explicit** memory is for "knowing *what*" whereas **Implicit** memory is for "knowing *how*".
- **Implicit memory examples** are: Driving, tying shoe-lace, brushing teeth, swimming etc - where a conscious awareness is not required BUT still the task is done.
- **Semantic memory** (for words, rules and language) examples are: remembering the capital of France, or the rules of chess, or the famous dialogue from a movie etc.
- **Episodic memory examples**: Remembering of events - what happened on your first date? or what happened on the first day of medical college? etc.

Brain Areas Involved in Integration of Memory

1. **Explicit (declarative) memory**
 - **Short-term memory**: Hippocampus
 - **Working memory**: Prefrontal Cortex
 - **Long-term memory**: Various parts of neocortex
2. **Implicit (declarative) memory**
 - **Neocortex**: Priming (Priming is recognition of words or objects by prior exposure to them, e.g. improved recall of a word when presented with the first few letters of the word)
 - **Striatum**: Procedural memory (skills and habits, which once learned become unconscious and automatic).
 - **Amygdala**: Associative learning (classical and operant conditioning - learning about relation between one stimulus and another).
 - **Amygdala**: Emotional responses.
 - **Cerebellum**: Skeletal musculature/motor responses.
 - **Reflex pathways**: Non-associative learning (habituation and sensitisation).

EXTRA EDGE

- The "**hippocampus**" acts as a sort of "**switching station**" between short-term and long-term memory.

Calculating V/Q ratio

- If alveolar ventilation is 4L/min and cardiac output is 5 L/min, then **V/Q ratio = 4/5 = 0.8**.
- In areas of "**dead space**" (i.e. areas that are ventilated BUT not perfused, ex. pulmonary embolus) the V/Q ratio is **infinity** (because V/zero = infinity; mathematically anything divided by zero = infinity).
Dead Space V/Q ratio = Infinity
- In areas of shunt (i.e. areas that are perfused BUT not ventilated, ex. physiologic shunt such as an inhaled foreign body or anatomical shunt such as right-to-left shunt) the V/Q ratio is zero (since 0/Q = zero; mathematically dividing zero by any number is always zero)
Shunt V/Q ratio = Zero

ENZYMES

- Enzymes are highly specialized **proteins** that act as catalyst in biochemical reactions.
- The word **enzymes** was coined by **Fredrick Cuhne** and means "**in yeast**".
- The only enzymes that is NOT a protein is **ribozyme** - Ribozyme is RNA with catalytic activity (e.g. Sn RNA in spliceosome).
- Abzymes** are **antibodies** with catalytic activity.
- Two types of enzymes are
 - Simple enzyme: Consists of only proteins
 - Complex enzyme (Holoenzyme) = protein part (apo-enzyme) + nonprotein part (coenzyme/cofactor/prosthetic group).

Coenzymes

- Coenzymes are usually **non protein organic** molecules that are **thermostable with low molecular weight**.
- A coenzyme can bond covalently or non-covalently to the enzymes. If **covalently bound**, then it is called a **prosthetic group**.
- In a group transfer reaction, coenzyme acts as either a donor or acceptor of the group and therefore serves a **second substrate (co-substrate)** e.g. pyridoxal phosphate in transamination of oxaloacetate to alpha ketoglutarate.

Examples of Coenzymes

Enzyme	Coenzyme
Transaminase, Decarboxylase	Pyridoxal phosphate (Vit B ₆)
Transketolase	Thiamine pyrophosphate (Vit B ₁)
Carboxylase	Biotin
Kinases	ATP/GTP
Dehydrogenases	NAD ⁺ /FAD

Cofactors and Prosthetic Groups

- Prosthetic groups are **nonprotein part** tightly bound to the enzymes by **covalent** bonds. **Metals** are the MC prosthetic groups. Enzymes which are tightly bound to metal are called metalloenzymes.
- MC cofactors are also metals

Metals as Cofactors and Prosthetic Groups

Metal	Enzymes
Zinc	Carbonic anhydrase, carboxypeptidase, alcohol dehydrogenase, alkaline phosphatase, ALA dehydratase, Lactate dehydrogenase
Magnesium	Phosphotransferase, mutase, enolase, phosphohydrolase, Glucose 6 phosphatase
Copper	Tyrosinase, Superoxide dismutase, Lysyl oxidase, amino acid oxidase, Cytochrome oxidase, Ferroxidase (ceruloplasmin)
Molybdenum	Xanthine oxidase, sulfite oxidase
Manganese	Enolase, Arginase,
Iron	Succinate dehydrogenase
Calcium	Lipase, Lecithinase
Selenium	Glutathione peroxidase

EXTRA EDGE

- IUBMB** classification of enzymes = International Union of Biochemistry and Molecular Biology classification.
- In IUBMB classification enzyme code number (EC number) consists of **4 digits**.
- First** digit denotes the '**main class**'.
- Second** digit gives the '**subclass**' (type of group involved in reaction)
- Third** digit denotes '**sub-sub-class**' (substrate on which enzyme acts)
- Fourth** digit is '**serial number**' of the enzyme.
- Example: Hexokinase number is 2.7.1.1

CLASSIFICATION OF ENZYMES

Enzymes class no. and enzyme class	Types of reaction catalyzed	Examples
I Oxidoreductases	Catalyze oxidation-reduction reactions i.e., transfer of electrons. One substrate is oxidised (loses electron) and the other substrate is reduced (accepts electron)	Dehydrogenases , DH (Alcohol DH, Glyceraldehyde-3-P-DH, malate DH, G-6-P-DH, pyruvate DH, lactate DH, succinate DH) Oxidases (L-Amino acid oxidase, cytochrome oxidase, xanthine oxidase, tyrosinase); Hydroperoxidases (Catalase, Peroxidase) Oxygenases Mono-oxygenase (phenylalanine hydroxylase, cytochrome P450) Dioxygenase (Homogentisate oxidase, Tryptophan pyrrolase, Nitric Oxide synthase)
II Transferases	Transfer functional group other than hydrogen from one substrate to another	Kinases (Hexokinase, glucokinase, pyruvate kinase) Transaminase (SGOT-AST and SGPT-ALT) Transmethylase, transketolase, transcarboxylase Cholineacetyl transferase
III Hydrolases	Hydrolases catalyze hydrolytic cleavage (make use of water) of C-C; C-O and C-L bonds and other covalent bonds. These enzymes are commonly found in digestive secretions and lysosomes	Esterases (Pseudocholinesterase) β -galactosidase Lipases Arginase Peptidases (pepsin, trypsin) Urease Acid phosphatase
IV Lyases	Lyases split substrate by non-hydrolytic process (by atom elimination, generating double bonds)	Aldolase Fumarase, Pyruvate decarboxylase Histidase Arginosuccinase HMG CoA lyase
V Isomerases	Isomerases catalyze interconversion of isomers of a compound (geometric or structural changes within the molecule)	Retinine isomerase Triosephosphate isomerase Racemase Mutase
VI Ligases	Ligases catalyze the joining together (ligation) of two molecules in reactions couples to hydrolysis of ATP	Synthetases (Argininosuccinate synthetase, Glutamine synthetase, PRPP synthetase, Carabamoyl phosphate synthetase) Acetyl CoA carboxylase

FACTORS INFLUENCING ENZYME ACTIVITY

Temperature

- Increasing temperature increases rate of reaction** by increasing kinetic energy and collision frequency of reacting molecules.
- Bell-shaped curve** is obtained by plotting temperature against velocity of reaction
- Highest activity of enzyme is at the **optimum temperature**—for most human enzymes this is between 35–40 deg C (37 deg C).
- Temperature coefficient (Q₁₀)**: It is the factor by which the rate of a reaction increases for a 10 deg C rise in

temperature. Most biological processes typically double for a 10 degrees rise in temperature - i.e, **Q₁₀ = 2**.

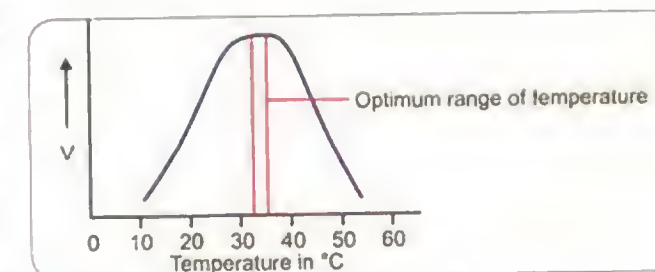


Fig. 4.1: Effect of temperature on velocity

Substrate Concentration

- For a fixed enzyme concentration, rate of reaction is directly proportional to the substrate concentration up to certain concentration of substrate (**saturation point**); after this further increase in substrate concentration does NOT increase the enzyme activity. The velocity of reaction at this stage is called **maximum velocity** (V_{max}).
- Hyperbolic** curve is obtained.

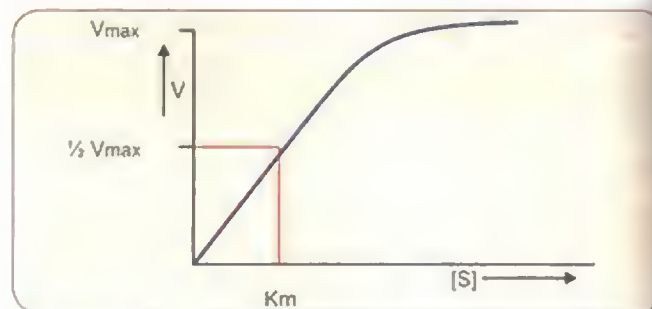


Fig. 4.2: Effect of substrate concentration (substrate saturation curve)

pH (Hydrogen Ion Concentration)

- Most intracellular enzymes exhibit optimal activity at pH values **between 5 and 9**.
- The relationship of enzyme activity to hydrogen ion concentration gives **bell-shaped** curve.

Michelis Menton Equation

- Michelis Menton equation describes how **velocity of reaction varies with substrate concentration**.

$$V_i = (V_{max} \times S) / K_m + S$$

where

- V_i = Initial velocity
- V_{max} = Maximum velocity
- S = Substrate concentration
- K_m = Michelis constant
- Michelis constant (K_m)** is defined as the substrate concentration required to produce **half maximum velocity of reaction** ($1/2 V_{max}$).
- Characteristics of K_m , Michelis constant are:
 - K_m is **independent of enzyme concentration**
 - K_m is **Unique** for each enzyme substrate pair - hence called **signature of enzyme**.
 - K_m is **Constant** for an enzyme
 - K_m **denotes affinity** of enzyme for the substrate - **lower the K_m , higher will be the affinity** for the substrate and vice versa.

Lineweaver Burke Plot

- A graphical representation of $1/S$ on X-axis and $1/V$ on Y-axis is called Lineweaver-Burke plot or **double reciprocal** plot.
- In this plot
 - X intercept is $1/K_m$
 - Y intercept is $1/V_{max}$
 - Slope is K_m/V_{max}

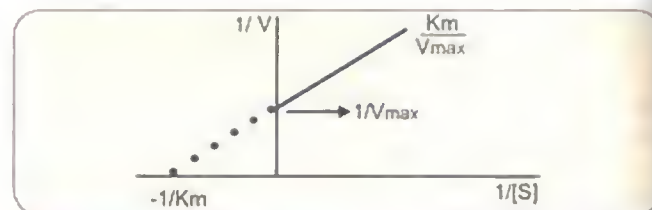


Fig. 4.3: Lineweaver-Burke plot

THEORIES OF MECHANISM OF ENZYME ACTION

- Michelis Menton theory
- Fisher's template theory
- Koshland's induced fit theory
- Lowering of activation energy.

ENZYME INHIBITION

Competitive	Non-competitive
Inhibitor will be structural analog of substrate	Inhibitor have NO structural analog of substrate (unrelated molecule)
Reversible	Irreversible
Excess substrate abolishes inhibition	Excess substrate DO NOT abolish inhibition
K_m increases	K_m remains the same
V_{max} remains the same	V_{max} decreases
Examples: Mostly drugs	Examples: Mostly poisons

EXTRA EDGE

- Memory Aid: "When you are **competitively** running (as in marathons) - you have to **increase the K_m** (Kilometres) and maximum velocity V_{max} should remain the same (it should not decrease)!"
- Almost all inhibitors of **electron transport chain** are irreversible non-competitive inhibitors.

Examples of Competitive Inhibitors

Drug	Enzyme inhibited	Clinical use
Statins	HMGCoA reductase	Lowering cholesterol
Warfarin	Vit K epoxide reductase	Anticoagulant
Allopurinol	Xanthine Oxidase	Gout
Penicillin	Transpeptidase	antibiotic
Sulfonamide	Pteroid synthetase	antibiotic
Trimethoprim	Dihydrofolate (FH_2 reductase)	antibiotic
Primaquine	FH_2 reductase	Malaria
Methotrexate	FH_2 reductase	Cancer
6-mercaptopurine	Adenyl succinate synthetase	Cancer
5-FU	Thymidylate synthetase	Cancer
Atazetidine	Phosphoribosyl amidotransferase	Cancer
Cytosine arabinoside	DNA polymerase	Cancer
Acyclovir	DNA polymerase	Antiviral
Neostigmine	Ach- esterase	Myasthenia
Alpha methyl dopa	DOPA decarboxylase	HTN
Oseltamivir (Tamiflu)	Neuraminidase	Influenza
Digoxin	Na^+-K^+ -ATPase	Heart failure

EXTRA EDGE

- Some competitive inhibitors which are not drugs are:
 - Oxamate inhibits *Lactate dehydrogenase*
 - Transaconitate inhibits *Aconitase*
 - Malonate inhibits *succinate dehydrogenase*

Examples of Non-competitive Inhibitors

Non-competitive inhibitor	Enzyme-inhibited
Cyanide	Cytochrome oxidase
Iodoacetate	Glyceraldehyde-3-phosphate
Fluoride	Enolase
HAL (British Anti Lewisite)	-SH group of many enzymes
Fluoroacetate	Aconitase
DIP (Di-isopropyl fluorophosphate)	Serine proteases
Arsenite	Alpha ketoglutarate dehydrogenase
Disulfiram (Antabuse)	Aldehyde dehydrogenase

Suicide Inhibition

- Special type of **irreversible** inhibition.
- The inhibitor makes use of the enzymes own reaction mechanism to inactivate it - **mechanism based inactivation**.
- Examples of suicide inhibition
 - Allopurinol inhibits xanthine oxidase
 - Treatment of trypanosomiasis by difluoromethyl ornithine inhibits ornithine decarboxylase
 - Aspirin inhibits cyclooxygenase

Feedback Inhibition

- Activity of the enzyme is inhibited by the final product of the biosynthetic pathway - feedback or **end-product inhibition**.
- Examples are:
 - Inhibition of **delta-ALA synthetase** by the end product heme (in heme synthesis)
 - AMP inhibiting first step in **purine synthesis**
 - Inhibition of **aspartate transcarbamoylase** by CTP.

Allosteric Regulation

- Allosteric enzyme has one catalytic site where the substrate binds and another separate allosteric site where the **modifier** binds.
- Binding of the modifier may activate or inhibit the enzyme.
- Examples of allosteric enzyme are given below.

Enzyme	Activator	Inhibitor
Phospho-fructokinase	Fructose 2,6-biphosphate	Citrate
Carbamoyl phosphate synthase-1	N Acetyl Glutamate (NAG)	
ALA synthetase		Heme
Aspartate trans-carbamoylase	ATP	CTP
HMG CoA reductase		Cholesterol
Pyruvate carboxylase	Acetyl CoA	ADP
Acetyl CoA carboxylase	Citrate	Acyl CoA

Measurement of Enzyme Activity

- Unit of enzyme activity:** One unit of enzyme activity is defined as the amount causing transformation of 1.0 mmol of substrate at **25 deg C** under optimum conditions of measurement.

- **Specific activity** refers to the number of enzyme units per milligram of protein.
- **Turnover number** refers to the number of substrate molecules transformed per unit time by a single enzyme molecule.
- **Catalase** has the **highest turnover number** and hence is the **fastest active enzyme**. (2nd fastest is carbonic anhydrase)

Therapeutic Uses of Enzymes

Enzyme	Therapeutic application
Aspraginase	ALL
Streptokinase	To lyse intravascular clot
Urokinase	To lyse intravascular clot
Papain	Anti-inflammatory
Alpha-1 antitrypsin	AAT deficiency; emphysema
Streptodornase	DNAase applied locally
Pancreatin (trypsin and lipase)	Pancreatic insufficiency

Enzymes Used for Diagnostic Purposes

Enzyme	Used for testing
Urease	Urea
Uricase	Uric acid
Glucose oxidase	Glucose
Peroxdase	Glucose, cholesterol
Hexokinase	Glucose
Cholesterol oxidase	Cholesterol
Lipase	Triglycerides
Restriction endonuclease	Southern Blot, RFLP
Reverse transcriptase	PCR
Horseradish peroxidase	ELISA
Alkaline phsophatase	ELISA

AMINO ACIDS

Basics of Amino Acids

- There are **20 amino acids** involved in the formation of proteins in the human body.

Classification of Amino Acids

Category	Amino acids
Based on nutrition	
Semi Essential Aa's	<u>Arg</u> inine (Arg); <u>His</u> tidine (His)
Essential Aa's	<u>I</u> soleucine (Ile); ; <u>L</u> eucine (Leu); <u>T</u> ryptophan (Try); <u>L</u> ysine (Lys);; <u>M</u> ethlonine (Met); <u>P</u> henylalanine (Phe); <u>T</u> hreonine (Thr); <u>V</u> aline (Val). <u>M</u> nemonic: ("Any <u>H</u> elp In <u>L</u> earning <u>T</u> hese <u>L</u> ittle <u>M</u> olecules <u>P</u> roves <u>T</u> ruly <u>V</u> aluable")

- Each amino acid has an **amino** group (NH₂) and a **carboxyl** group (COOH) attached to the **alpha carbon** atom (αCH, also called "**chiral**" carbon atom) and a variable **side chain (R)**. Most amino acids are **alpha** amino acids.
- Chirality means that amino acids (**except glycine**) can exist as two stereo-isomers (enantiomers) named D and L.
- All amino acids found in proteins are of **L-configuration**.
- **D-amino acids** are rare and are present in **bacterial cell walls**.
- **Non- alpha** amino acid - either carboxyl or amino group is **NOT** attached to the alpha carbon atom. Such amino acids in tissues are: β-alanine; β-aminoisobutyrate and γ-aminoisobutyrate.
- The **side chains** vary in length and complexity and determine the characteristics of each amino acid.
- **Imino acid** - here the amino group is NOT free; the nitrogen of amino group is inside the **pyrrolidine ring**, e.g. **Proline** is imino acid. It **has NH group** instead of NH₂ group.

Dissociation of Amino Acids

- Amino acids are dipolar ions (**zwitter ions** or **ampholytes**); they carry a positive charge at one end and a negative charge at other end of the molecule.
- The carboxyl group ionises at physiological pH forming an anion (COO⁻) and the amino group becomes a cation (NH₃⁺).
- **Polar** Aa (being **hydrophilic** - **form hydrogen bonds with water**) are distributed on the **surface** of the protein whereas **non-polar** Aa being **hydrophobic** are distributed within the protein (**lipophilic**).
- Thus in **transmembrane proteins**, **nonpolar Aa** are embedded in the lipid bilayer while **polar Aa** are present outside or inside the membrane.
- **Isoelectric pH**: The pI at which amino acid becomes zwitter ion, i.e bears no net charge and thus does not migrate to anode or cathode is called **Isoelectric pH**. At isoelectric pH an amino acid acts as a zwitter ion and does not move in an electric field.

Contd...

11

Category	Amino acids
Metabolic classification	
Ketogenic Aa's	Leu (purely ketogenic), Lys
Gluicogenic Aa's	14 amino acids: Met, Val, Ala, Arg, Asparagine Aspartate, Cysteine, Glutathione, glutamic acid, Gly, His, Proline, Serine, Thr,
Glucogenic/Ketogenic Aa's	Phe, Ile, Tyr, Thr (" PITT ")
Based on chemical nature	
Acidic Aa's	Aspartic acid (aspartate, lowest isoelectric point) Glutamic acid (glutamate) Both are Monoamino-dicarboxylic acids
Basic Aa's	His Arg (most basic, highest isoelectric point), Lys (" HAL ")
Based on side chains	
Sulfur containing Aa's	Methionine , Cysteine , Cystine ("Sulfur is MeCCy ")
Aromatic Aa's	Histidine , Phenylalanine , Tyrosine , Tryptophan (" His PheTT (feet) have aroma")
Aa's with ALi phatic side chains	Alanine , Leucine , Isoleucine , Glycine , Valine (" ALI-GV , ALI's Gift Voucher ")
Aa's with hydroxyl (OH) groups	Serine , Threonine , Tyrosine (" OH! - ShiTT! ")
Aa's with amide groups	Asparagine, Glutamine
Others	
Imino acids	Proline (" I'm Pro !")
1st Aa	Selenocystiene (coded by UGA stop codon) (" At 21, U Go Away from home! "); structure similar to cysteine; present in glutathione peroxidase and delodinase.
2nd Aa	Pyrrolysine (by UAG stop codon) On basis of Polarity
Hydrophilic (polar) Aa's	Aa having side chains containing functional groups such as carboxyl, amino, amide, and hydroxyl groups are polar. Negatively charged (acidic - carboxyl side chain): Aspartate; Glutamate Positively charged (basic - amino side chains): " HAL " as above Uncharged (neutral - hydroxyl or amide side chains): Asparagine, Glycine, Cysteine, glutamine, serine, threonine, tyrosine
Hydrophobic (Non-polar) Aa's	The more alkyl groups that are present, the more non-polar the amino acid will be. Phenylalanine is the most non-polar Aa Examples are: Aliphatic side chains: " ALI-GV " as above Aromatic side chains: Histidine, Tryptophan

EXTRA EDGE

- Normally Aa do not absorb visible light and are thus colorless.
- Aromatic Aa absorb **high wavelength (280 nm, 250-290 nm)** **UV light**. **Tryptophan** has the highest absorption maximum.

Glycine (Gly)

- Glycine is **simplest** and **smallest** Aa.
- Gly is Aa with **NO optically active carbon** (i.e, **no 'chiral' carbon**) - hence **optically inactive**.
- Gly has hydrogen as side chain instead of carbon side chain - accounts for much **more** conformational

flexibility in Gly - it is therefore a *good agent for turns* in polypeptides and proteins.

- Gly is *synthesised from glyoxylate, glutamate and alanine*.
- Gly participates in synthesis of:
 - **Heme** = Gly + Succinyl CoA
 - **Creatinine** = Gly + Arginine (in kidney) → Guanidinoacetic acid (ME (thionine) thylated to) → Creatine. ("GLARME")
 - **Glutathione** = Gly + Cysteine + Glutamic acid.
- Conjugates of glycine:
 - Benzoic acid + Glycine = **Hippuric acid**.
 - Cholic acid (Bile acid) + Glycine = **Glycocholic acid**.
- Every third Aa in **collagen** is glycine.
- Gly contributes to **purine ring**.
- **Sarcosine** is methyl glycine.
- **Betaine** is trimethyl glycine.
- Gly is both *excitatory and inhibitory neurotransmitter*.

Functions of glutathione

- Glutathione is a **tripeptide** of glycine, cysteine and glutamic acid.
- The **sulphydryl group** of cysteine residue is the reactive portion of glutathione which can undergo oxidation and reduction.
- **Reduction of methemoglobin** (keeps iron in ferrous state by reduced glutathione)
- Free radical scavenging (antioxidant) as **glutathione peroxidase**.
- **Meister's cycle** or gamma glutamyl cycle: *absorption of neutral amino acids*.
- Forms **conjugates with xenobiotic species**.

Histidine (His)

- His contains **imidazole** group - this accounts for **maximum buffering capacity at physiological pH and neutral range (7.0 - 7.4)** - i.e. it can accept or donate a proton (protonate or deprotonate). Thus, **local milieu** has maximum on ionization has maximum influence on histidine.
- His undergoes decarboxylation to give **histamine**
- In **folic acid deficiency**, the His derivative **FIGLU** is excreted in the urine
- **RBC and liver** contain a histidine derivative called **ergothioneine** (reducing substance)
- His gives **urocanic acid**
- In normal pregnancy, **histidinuria** occurs, but this does not occur in toxemia

Alanine (Ala)

- Alanine is synthesized *from pyruvate* by **transamination**.
- Ala has **methyl** side chain and is **non-polar**.
- Ala transports amino group from **skeletal muscle**.
- Ala Participates in glucose-alanine cycle (**Cahill cycle**).
- Ala is a component of **pantothenic acid** (hence a component of **CoA**).
- Ala is **increased** in blood during **starvation**.

EXTRA EDGE

- **Beta alanine** is a naturally occurring **beta-amino acid** (in which amino acid is at the beta-position, i.e. 2 carbon atoms away from the carboxyl group).
- It is NOT used in the biosynthesis of major proteins or enzymes.
- Beta alanine is *formed in-vivo* from **cytosine** and **dihydro-uracil**.
- Beta alanine is a component of *naturally occurring peptides*:
 - **Carnosine** (histidine + beta alanine) and **anserine** (N methyl carnosine) - both are present in **skeletal muscle**.
 - **Pantothenic Acid**
 - Coenzyme A
 - Acyl carrier protein
- **Homocarnosine** is GABA + histidine.

Lysine (Lys)

- **Lys** is **deficient in cereals**; it is the **limiting amino acid in wheat**.
- Represented by the letter **K**. **saccharopine** is an intermediate in the lysine catabolic pathway
- **Hydroxylysine** is a constituent of **collagen**.
- Lys along with methionine (SAM is the methyl donor) are the precursors of **carnitine**
- Bacterial putrefaction (decarboxylation) of Lys forms **cadaverine**.

Tryptophan (Try)

- Special group present is **indole** group.
- **Tryptophan hydroxylase** is the rate limiting step in **serotonin and melatonin synthesis**.
- **Try** is catabolized by **Kynurenine-Anthranilate** pathway
- Specialised products from tryptophan are
 - Niacin
 - Melatonin
 - Serotonin
- **60 mg** of Try is converted to **1 mg** of Niacin.

EXTRA EDGE

- **Blue diaper syndrome (Drummond syndrome)**: Due to bacterial breakdown of unabsorbed **tryptophan** (from intestine) into indican and indigo blue.

Aspartic Acid (Aspartate)

- **Transamination of oxaloacetate** forms Aspartate.
- Aspartate contributes for **urea synthesis**, **purine synthesis** and **pyrimidine synthesis** (mainly).
- **Canavan disease** is due to high concentrations of **N-acetyl aspartic acid**; severe leukodystrophy of white matter of brain.

Methionine

- **Methionine** gives **spermidine**: Present in ribosomes and sperm.
- **Outsthouse syndrome**: Malabsorption of methionine and neutral Aa's.

Serine

- Serine is used for formation of **cysteine**, **ethanolamine**, **choline**, **betaine**.
- **Drugs with serine** as analog are **cycloserine** and **azaserine**.

Cysteine

- Specialized products *derived from cysteine*: Coenzyme A (CoA); Taurine, Glutathione; Betamercaptoethanolamine
- Cysteine is present in **scleroproteins**—keratin of skin, hair and nails
- Cysteine is oxidized to cysteic acid and then decarboxylated to form **taurine**. **Taurine** is used for **conjugation of bile acids**.

Cystine

- Condensation of two cysteine with **disulphide bonds** gives cystine.

Arginine

- Functions of **arginine**: Synthesis of **Nitric oxide**, **agmatine** and **creatine**.

Tyrosine

- Special products obtained from **tyrosine** are:
 - Melanin
 - Catecholamines
 - Thyroxine
- **Tyrosine hydroxylase** is the **rate limiting step** in **catecholamine synthesis**
- **Catecholamines** are dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline).

Important MCQ Points about Amino Acids

- **Arg** and **His** are required during periods of **growth**.
- **Asp** and **Glu** are **most active of all Aa's** in metabolism.

- **Glutamine** is **most abundant Aa in blood**; yields - **GABA** and **Glutathione**.
- **Leucine**: **Most potent ketogenic** amino acids; **HMG CoA** is formed in the metabolism of **leucine**
- **During starvation**, **brain utilizes ketone bodies** as fuel (**b-hydroxybutyrate**); it also utilizes branched chain amino acids, particularly **Valine**
- **MC Aa** that undergoes **oxidative deamination** is **glutamic acid**; Glutamic acid → **alpha ketoglutarate**
- Asparagine → aspartate → **oxaloacetate**.
- Aa that **decreases aging**: Cysteine, taurine.
- Aa that **accelerates aging**: Homocysteine
- **Vitamins required for metabolism of sulphur containing Aa's** are **vitamin B₁₂**; **folic acid** and **vitamin B₆**.
- In **vit B₁₂ deficiency**, homocysteine cannot be converted to methionine; hence **homocysteine accumulates** and is risk for **acute coronary syndrome**.
- Enzymes with **tetrahydrobiopterin** as coenzyme are: **phenylalanine hydroxylase**; **tyrosine hydroxylase**; **tryptophan hydroxylase**; **Nitric Oxide synthase**.
- The major end product of **epinephrine** and **norepinephrine** is **vanillyl mandelic acid (VMA)**
- Major end product of **dopamine** is **Homovanillic acid**.
- **Proline** and **Hydroxyproline** will NOT allow the formation of **α-Helix**.

Color Reactions of Amino Acids

Color reactions	Test answered by
Xanthoproteic test (conc. nitric acid is reagent)	Aromatic Aa (Phenylalanine, tyrosine, tryp (tophan); yellow color due to formation of picric acid
Millon's test	Tyrosine (phenol)
Sakaguchi test	Arginine (Guanidinium group)
Sulphur test	Cysteine
Cyanide Nitroprusside test	Cysteine, Homocysteine
Pauly's test	Histidine (imidazole) Tyrosine (phenol)
Aldehyde test Acree Rosenheim test (Glyoxylic acid is used) Hopkin's Cole Test (Formaldehyde and mercuric sulphate is used)	Tryptophan (Indole group)

EXTRA EDGE

- **Biuret test**: Cupric ions in alkaline medium turns **violet** with peptide bond nitrogen. (**minimum of 2 peptide bonds** required).
- **Ninhydrin test**: General test for all alpha Aa's. **Purple** color is due to Ruhemann's purple.



Fig. 4.4: Biuret test

Specialized Products from Individual Amino Acids

Tryptophan	<ul style="list-style-type: none"> Niacin Serotonin Melatonin
Tyrosine	<ul style="list-style-type: none"> Melanin Catecholamines (Epinephrine, Norepinephrine, Dopamine) Thyroxine
Glycine	<ul style="list-style-type: none"> Glutathione Heme Creatinine Heme
Cysteine	<ul style="list-style-type: none"> Cystine Taurine Beta-mercaptoethanolamine
Arginine	<ul style="list-style-type: none"> Nitric Oxide
Histidine	<ul style="list-style-type: none"> Histamine FIGLU
Glutamate	<ul style="list-style-type: none"> N Acetyl glutamate GABA
Aspartate	<ul style="list-style-type: none"> Purine Pyrimidine Urea synthesis

AMINO ACID METABOLISM

- Catabolism of amino acids (biosynthesis of urea) take place in the below 4 steps. Ammonia is detoxified by liver cells to **urea** and excreted through the kidney.

1. Transamination
2. Deamination
3. Transport of Ammonia
4. Reactions of urea cycle

1. Transamination

- Transamination** is the **reversible** transfer of an **amino group** from an **amino acid** to a **keto acid** with **pyridoxal phosphate** as coenzyme.
- Transamination occurs in **all tissues** and plays an important role in **biosynthesis of nutritionally non essential amino acids**.
- NO** free ammonia is liberated.
- Transamination occurs via double displacement (**ping-pong**) mechanism.
- Amino acids that **DO NOT** undergo transamination: **Lysine, Threonine, Hydroxyproline, Proline** ("Lying Thief Hydes from Police").

Examples of transamination

- Alanine aminotransferase (**ALT**) or Serum Glutamate Pyruvate Transaminase (**SGPT**). It catalyses
 - L-Alanine + alpha ketoglutarate \leftrightarrow Pyruvate + L-Glutamate
- Aspartate aminotransferase (**AST**) or Serum Glutamate Oxaloacetate Transaminase (**SGOT**). It catalyses
 - L-Aspartate + alpha ketoglutarate \leftrightarrow Oxaloacetate + L-Glutamate

2. Deamination

- The **removal of amino group (NH_2 group)** from Aa is called deamination; a **reversible** reaction.
- Maybe oxidative or non-oxidative.
- Oxidative deamination**
 - MC Aa** that undergoes oxidative deamination is **glutamic acid (glutamate)**.
 - L-Glutamate dehydrogenase (GDH)** is the enzyme responsible; **NAD⁺ or NADP⁺** is the **coenzyme**.
 - Releases nitrogen as ammonia which enters the urea cycle.
 - Occurs primarily in the **liver** - liver mitochondria contain GDH.
- Non-oxidative deamination**
 - L-amino acid oxidase plays role in minor pathway of deamination of amino acids
 - Takes place in liver and kidney
 - FMN is the co-enzyme
 - H₂O₂** is formed.

Examples are:

- Amino acid dehydrases for Aas with hydroxyl group (serine, threonine)
- Histidase for histidine
- Amino acid desulfhydrases for Aas with sulfhydryl group (cystine and homocysteine).

EXTRA EDGE

- Transdeamination** = transamination + oxidative deamination

1. Transport of Ammonia

- Free ammonia generated all over the body has to be detoxified (since it is toxic to brain) and sent to liver to enter the urea cycle.
- Transport of ammonia from **most of the tissues including brain** is in the form of **glutamine**.
- Transport of ammonia from **skeletal muscle** is in the form of **alanine**.
- Urea** is the major end product of protein metabolism in the body.

4. Reactions of Urea Cycle

- Reactions of Urea cycle is given below in detail as a separate topic

UREA CYCLE

- A.k.a. **Ornithine cycle** or **Krebs-Henseleit cycle**.
- Site of urea cycle: **Liver; Both** in the **mitochondria** (first 2 reactions) and **cytoplasm** (rest of reactions).
- Memory Aid: All enzymes in cytoplasm in urea cycle starts with letter "A"!
- Compounds consumed in urea cycle are **CO₂, NH₄⁺ and aspartate**.
- Compound that enters into urea cycle and is regenerated again - **ornithine** (hence also called ornithine cycle!)
- 2 ATPs are used in the formation of carbamoyl phosphate and 2 ATPs are used in the formation of argininosuccinate. Thus urea cycle **consumes 4 ATP** (3 ATP directly).
- The overall reaction of urea cycle may be summarized as

$$\text{NH}_4^+ + \text{CO}_2 + \text{Aspartate} \rightarrow \text{urea and fumarate.}$$
- The above reaction implies that in the urea cycle: **Aspartate is consumed; fumarate is a byproduct**; there is **NO net loss or gain of ornithine, citrulline, argininosuccinate and arginine**.

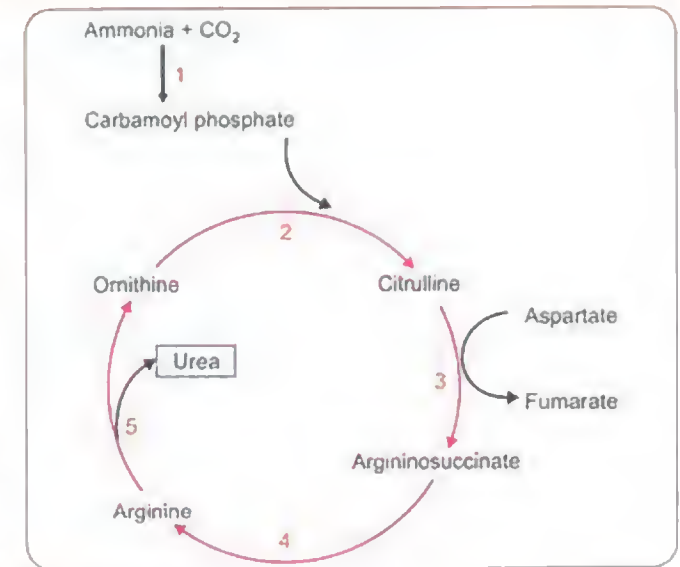


Fig. 4.5: Urea cycle, summary

- Enzymes of the urea cycle are (indicated by the numbers in above figure)

1. Carbamoyl Phosphate Synthetase-1 (CPS-1):

- CPS-1 catalyzes formation of **carbamoyl phosphate**
- CPS-1 is **rate limiting enzyme** of urea cycle.
- CPS-1 is active only in the presence of **N-acetyl glutamate**, an **allosteric activator**

2. Ornithine transcarbamoylase (OTC):

It catalyses formation of citrulline from carbamoyl phosphate and ornithine

3. Argininosuccinate synthetase:

It is a **ligase**.

4. Argininosuccinate lyase

5. Arginase (it is a hydrolase):

Causes **hydrolytic cleavage** of arginine to release urea and ornithine (which re-enters the mitochondria).

EXTRA EDGE

- Source of nitrogen atoms of urea: One from **ammonia** and one from amino group of **aspartate**.
- Urea bicycle**: Urea is linked to TCA cycle through fumarate and aspartate - hence called urea bicycle.

UREA CYCLE DISORDERS

- All urea cycle disorders are characterized by
 - Hyperammonemia
 - Encephalopathy
 - Respiratory alkalosis.
- Treatment of urea cycle disorders consist of

- **"Removal of Ammonia by Nitrogen scavengers"** (by acylation with Sodium benzoate; Sodium phenylacetate; Sodium phenylbutyrate; Glycerol phenylbutyrate) — these drugs divert nitrogen away from the urea cycle by promoting the synthesis of nitrogen-rich metabolites which are excreted at high rates in the urine.

Aginine Supplementation (Provides ornithine)

Disease	Enzyme-deficient	Comments
Urea Cycle Disorders due to enzyme deficiency		
Hyper-ammonemia type 1	CPS-1	(Carbamoyl phosphate synthetase)
Hyper-ammonemia type 2	OTC - Ornithine trans-carbamoylase	ONLY X-linked (partially dominant) urea cycle disorder; all others are AR MC urea cycle disorder; Orotic aciduria occurs (pink urine stones)
Citrullinemia type 1 (classic)	Argininosuccinate synthetase	
Argininosuccinic aciduria	Argininosuccinate lyase	Trichorrhexis nodosa (dry and brittle hair)
Hyper-argininemia	Arginase	Causes least hyperammonemia; progressive spastic diplegia may occur
Urea Cycle Disorders due to transporter defect		
Citrullinemia type 2	Citrin (aspartate glutamate carrier protein) defect	located on chromosome 7q
HHH syndrome	Ornithine Permease; ORNT-1 gene defect	Hyperornithinemia-Hyperammonemia-Homocitrullinuria.

HYPERPHENYLALANINEMIAS

Phenylketonuria (PKU)

- MC disorder of amino acid metabolism.
- AR, **chromosome 12** affected

Type	Enzyme deficiency
Classical (type 1) PKU	Phenylalanine hydroxylase
Nonclassical / Atypical (type 2 and type 3) PKU	Dihydrobiopterin reductase
Type 4 and type 5 PKU	6-pyruvyl tetrahydropterin deficiency or Guanosine triphosphate (GTP) cyclohydrolase deficiency (enzymes that synthesise BH4 - tetrahydrobiopterin)

- In PKU there is **inability of oxidation** of phenylalanine into tyrosine.
- Thus tyrosine becomes essential and phenylalanine builds up in blood (**hyperphenylalaninemia**) and this is metabolized to **phenylketones** (**phenylpyruvate** and **phenylacetate**) that is excreted in urine.
- Clinical Findings:
 - Infant is normal at birth. If untreated:
 - Profound **mental retardation** occurs
 - **Growth retardation**
 - **Fair hair** and **fair skin** (**Phe** is a competitive inhibitor of tyrosinase - so no melanin in skin!!), **eczema**,
 - **Microcephaly**, **hyperactivity**, **seizures**.
 - **Musty or Mousy odor** of skin, hair and urine due to **phenylacetic acid**.
 - Serum Phe is elevated, serum Tyr is normal or low.
- Screening Tests
 - **Tandem mass spectrometry** - investigation of **choice** now (detects Phe in serum)
 - **Guthrie's test** (detects Phe in serum)
 - **Ferric chloride test** (**Phe** in urine gives green color with FeCl₃)
- Treatment:
 - **Low-phenylalanine** diet
 - Administration of large neutral amino acids (**LNAAs**) - Tyr, Try, Leu, Iso, Val, Met, His, Lys, Thr and Phe.
 - **Sapropterin** dihydrochloride (Kuvan) - synthetic form of BH4 - FDA approved to reduce phenylalanine levels in PKU.

DISORDERS OF TYROSINE METABOLISM

Disease	Enzyme-deficient	More Info
Type 1 (First) Tyrosinemia (Hepatorenal)	Fumaryl acetoacetate	"Boiled Cabbage" odour; liver failure, cirrhosis, peripheral neuropathy. Treatment: Nitisinone
Type 2 (Two) Tyrosinemia (Oculo-cutaneous)	Tyrosine Transaminase	Polymplanter kerotosis, painful corneal erosions with photophobia
Type 3 (neonatal) Tyrosinemia	Para hydroxy phenyl pyruvate hydroxylase (4-hydroxy phenyl pyruvate dioxygenase)	Hypertyrosinemia with normal liver function

Contd...

Contd

Disease	Enzyme-deficient	More info
Hawkinsinuria	Para hydroxy phenyl pyruvate hydroxylase (4-hydroxy phenyl pyruvate dioxygenase)	"Swimming Pool odor" ; Transient failure to thrive, metabolic acidosis in infancy
Alkaptonuria	Homogentisic acid oxidase	Discussed separately below
Albinism (oculocutaneous)	Tyrosinase	Hypopigmentation of hair, skin and eyes/optic fundus; photophobia; visual loss

Alkaptonuria (Ochronosis)

- AR; **Congenital deficiency** of **homogentisic acid oxidase** in the degradative pathway of tyrosine.
- Resulting **alkapton bodies** cause **urine to turn black on standing**, **connective tissue is also dark**.
- May have debilitating **arthralgias**; **intervertebral disc calcification in lumbar area**, **cartilage of nose/ pinna etc..** (**Ochronosis**).
- **Nitisinone** is under research for treating alkaptonuria (approved for **hereditary tyrosinemia type 1**)

DISORDERS OF SULFUR CONTAINING AMINO ACIDS

Homocystinuria

- AR; **Cystothionine beta synthase deficiency** (homocystine is not converted to cysteine)
- Disorder of methionine metabolism and leads to **hyperhomocysteinemia** (in plasma and urine).
- **Mental retardation**.
- **Osteoporosis**, tall stature, kyphosis,
- Homocystinuria = **Infero** Nasal lens subluxation.
- **Atherosclerosis** and thrombosis (stroke and MI, caution with Gen. Anesthesia).
- **Cyanide nitroprusside test** is done on urine
- Treatment: Pyridoxine - vitamin B₆ is the drug of choice (along with vitamin B₁₂ and folate in diet)

Cystinuria

- Inherited **defect of dibasic amino acid transporter** for **Cystine, Ornithine, Lysine** and **Arginine (COLA)** in the **PCT of the kidneys**.
- Excess cystine in urine causes **cystine kidney stones** (**radiopaque**, relatively **resistant** to lithotripsy)

- Treatment is with **acetazolamide** to alkalinize urine.
- **Garrod's tetrad**: Cystinuria; albinism; alkaptonuria; pentosuria.

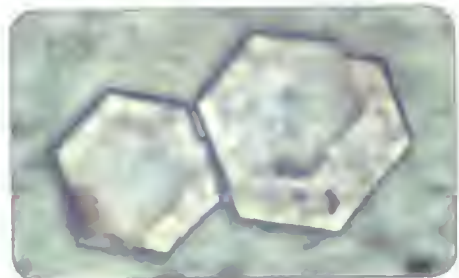


Fig. 4.6: Cystine crystals in urine

Cystinosis

- Do not confuse "cystinosis" with "cystinuria": they are different diseases.
- **Nephropathic cystinosis** (MC type) is an **autosomal recessive lysosomal storage disorder** caused by defective transport of the amino acid cystine out of lysosomes in the **PCT of the kidneys**.
- Presents in **first year of life** with **polyuria**, **polydipsia**, **dehydration**, **vomiting**, **metabolic acidosis**.
- Complications: **Renal Fanconi's syndrome**, **rickets**, **photophobia**, **hypotonia**, **renal failure**, **corneal cystine crystals**.
- Treatment: **Cysteamine bitartrate** and kidney replacement.

DISORDERS OF BRANCHED CHAIN AMINO ACIDS

Maple Syrup Urine Disease

- Deficiency of **branched chain α-keto acid dehydrogenase (BCKAD)** results in defective **oxidative decarboxylation** of branched chain amino acids - **Leu, Ile** and **Val** and their levels are increased in plasma and urine - **Branched chain ketonuria**.
- Causes **severe CNS defects**, **mental retardation** and **death**.
- **Burnt sugar odor** of urine - urine smells like **maple syrup**.
- Treatment: Restrict branched chain Aa's and give high doses of **thiamine**.

Isovaleric Acidemia

- Defect of metabolism of **branched chain amino acids** (**leucine, isoleucine, valine**),
- **Isovaleryl CoA dehydrogenase** deficiency

- **Cheesy odor of breath** and body fluids.
- **"Sweaty feet"** odor of urine
- Treat by administering **glycine**.

OTHER DISEASES

Hartnup Disease

- AR, **pellagra-like** skin lesions, **neuro-psychiatric** manifestations, and **neutral aminoaciduria**.
- Clinical features result from decreased absorption of **tryptophan and neutral Aas** (caused by intestinal and renal malabsorption) and associated **niacin** deficiency.
- Defective protein is **SLC6A19**
- **Obermeyer** test (for **indole/indican in urine**) is positive.
- **High protein diet** helps in treatment.

Canavan Disease

- AR; MC in Ashkenazi **Jews**.
- Deficiency of **aspartoacylase** leading to increased excretion of N-acetylaspartic acid in urine.
- Leads to **leukodystrophy**.

Inborn error of metabolism	Urine odor
Maple syrup urine disease	Maple syrup (Burnt sugar)
Hawkinsinuria	Swimming pool
Isovaleric acidemia, glutaric acidemia	Sweaty feet
Tyrosinemia; Hypermethioninemia	Boiled cabbage (rancid butter)
Phenylketonuria	Musty (mousey)
Trimethylaminuria	Rotting fish
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like

EXTRA EDGE

- **Dried blood spot (DBS)** testing has been used for screening for **inborn errors of metabolism** since 1960s. Also used for screening for **congenital hypothyroidism**

ONE CARBON METABOLISM

- Groups containing **single carbon atom** are called one carbon groups. These may be *derived from the following Aa's during their metabolism (serine, histidine, glycine, tryptophan)*.
- One-carbon metabolism exists because one-carbon groups are **too volatile** and need to be attached to something before being processed.
- One-carbon groups encountered in biological reactions are
 - **Methyl** (-CH₃)

- **Hydroxymethyl** (-CH₂OH)
- **Methylene** (-CH₂)
- **Methenyl** (-CH)
- **Formyl** (-CH-O)
- **Formimino** (-CH-NH)
- **Carbon dioxide** (-CO₂)

- There are three ways of moving one-carbon groups using the following molecules:
 1. **Tetrahydrofolate (THF)** as a cofactor in enzymatic reactions - **most versatile one-carbon donor** in biosynthetic reactions THF is derived from **vitamin B₁₂**.
 2. **S-adenosylmethionine (SAM)** as a methyl (-CH₃) donor.
 3. **Vitamin B₁₂ (Cobalamin)** as a co-enzyme in methylation and rearrangement reactions.

CLASSIFICATION OF PROTEINS

Based on Shape of Proteins

Fibrous protein	Globular protein
Elongated/needle shaped/ cylindrical/rod like	Spherical/oval/spheroidal
Minimum solubility in water	Easily water soluble
Mainly structural proteins (collagen, elastin, keratin)	Metabolic proteins (transport proteins - albumin and globulin; Hb; myoglobin, antibodies, enzymes and hormones)

Based on Composition

- **Simple** proteins: Contain only amino acids (e.g. **albumin, globulin**).
- **Conjugated** proteins: Proteins + non-protein part (prosthetic group). Examples as below

Conjugated protein	Constituents	Example
Glycoproteins	Protein + carbohydrate	Blood group antigens, immunoglobulins, mucin of saliva, plasma proteins (except albumin, TSH, FSH, LH)
Lipoproteins	Protein + Lipids	LDL, HDL, VLDL, Chylomicrons
Nucleoproteins	Protein + nucleic acids	Histones
Phosphoprotein	Contains phosphorus	Casein of milk and vitellin of egg yolk

Contd...

Conjugated protein	Constituents	Example
Chromoprotein	Protein + colored prosthetic group	Hemoglobin (red); flavoprotein (riboflavin, yellow) and visual purple (vitamin A, purple)
Metalloprotein	Protein + metal ion	Tyrosinase (copper); carbonic anhydrase (zinc); cytochrome (iron)

STRUCTURE OF PROTEINS

- Proteins are linear, unbranched polymers of different amino acids
- The **peptide bond** is formed between the **α-carboxyl group (C-terminal)** of one amino acid and the **α-amino group (N-terminal)** of another.
- **Structure of protein** determines its **biological action**.

Primary Structure

- Primary structure is the **linear sequence of amino acids** (specific order of amino acids) held together by **peptide bonds** (a type of **covalent bond**). Amino acid sequence determines the **3D structure** of protein.

Secondary Structure

- Spatial relationships of **neighboring amino acid residues** contributes to secondary structure. Regular folding and twisting of the polypeptide chain brought about by **hydrogen bonding** is called secondary structure.
- Secondary structure of proteins include:
 - **Alpha-helix**
 - **Beta-pleated sheet**
 - **Loops; bends and turns.**

1. Alpha Helix

- Alpha-helix is the **MC** secondary structure.
- **Right handed** alpha helix is the **most stable** and MC secondary structure.
- All **intrachain hydrogen bonds** in alpha helix are **parallel** (i.e., in the same direction).
- There are **3, 6 amino acyl residues** in each turn of the alpha helix.
- The **pitch** (vertical distance per turn) of the alpha helix is **0.56 nm** (5.6 Angstroms).

- **Proline disrupts alpha helix** because of geometric incompatibility of imino group of proline (it can only be stably accommodated within the first turn of an alpha helix).
- **Glycine** also tends to disrupt alpha helix due to its **high flexibility**.
- Examples of proteins with alpha helix as the major secondary structure: **Hemoglobin** and **Myoglobin**.

2. Beta Pleated Sheet

- Polypeptide chain is almost **fully extended**; they have a zig-zag or pleated pattern.
- **Glycine** is the main amino acid in beta pleated sheet; it produces **kinks**.
- Examples of proteins whose major structure is beta pleated sheet are: **Flavodoxin** (parallel); **silk fibroin** (anti parallel) and **carbonic anhydrase** (parallel and anti-parallel).

Super Secondary Structures (Motifs)

- Secondary structural elements (alpha helices and beta sheets) join to form **super secondary structures (motifs)**. Examples are
 - Beta-alpha-beta motif
 - Beta-meander motif
 - Beta barrel motif
 - Greek key motif
- **DNA binding motifs** are also examples of super secondary structures. Examples are
 - Zinc Finger motif
 - Leucine zipper motif
 - Helix turn helix motif

Protein	Structural motif present
Myoglobin	Alpha helix and beta pleated sheet
Collagen	Triple helix
Keratin	Coiled coil
Elastin	No specific motif
Superoxide simutase	Antiparallel beta pleated sheet

Tertiary Structure

- The **complete 3-D structure of a polypeptide** is the tertiary structure.
- Tertiary structure is maintained by the following bonds.
 - **Weak non-covalent hands (main):** Hydrogen bonds; hydrophobic bonds; electrostatic (ionic) bonds and Van der Waal's forces.
 - **Covalent disulfide bonds** have limited role.
- **Domains** are a type of tertiary structure.

- **Rossmann fold** is a domain seen in the family of oxidoreductases; they share a common N terminal (NADP+) binding region called Rossmann fold.

Quaternary Structure

- Quaternary structure is the **spatial relationship between individual polypeptide chains**, e.g. arrangement of subunits of **hemoglobin**.
- It describes the subunit composition of a functional protein.
- The MC number of subunits is 2 (dimer) or 4 (tetramer).
- The structure of **globular protein** in aqueous solution is compact, with a high density of the atoms in the core of the molecule. **Hydrophobic side chains are buried in the interior** whereas, **hydrophilic groups** are generally found on the **surface** of the molecule

Isopeptide Bond

- An isopeptide bond is an amide bond that is **not present on the main chain** of a protein.
- The bond forms between the carboxyl terminus of one protein and the amino group of a **lysine residue** on another (target) protein, e.g. the bond between the glutamyl residue and the cysteinyl residue of glutathione.
- Isopeptide bonds can be **either enzyme catalyzed or form spontaneously**.
- Spontaneous isopeptide bond formation is a stabilizing **posttranslational modification**.

PROTEIN DENATURATION

- Denaturation of proteins refers to **disruption of higher order structure** (secondary, tertiary and quaternary structure) of proteins, when treated with a denaturing agent.
- **Denaturing agents** are: mild heating; treating with 8M urea or 6M guanidine chloride; salicylates; heavy metal ions; trichloroacetic acid; physical agents (X-rays, UV rays; high pressure and vigorous shaking).
- Salient features of denaturation are:
 - **Primary structure (amino acid sequence)** is NOT altered.
 - **Peptide bond** (a strong covalent bond) **remains intact**.
 - **Loss of biological/functional activity**.
 - Loss of secondary, tertiary and quaternary structure with **random coil** formation.
 - Loss of folding.
 - **Randomisation of conformation** of polypeptide chain.

- Denaturation is generally **irreversible**
- Denatured proteins are **less soluble** and in many cases, they precipitate.

PRECIPITATION REACTION OF PROTEINS

- Solubility of proteins depends on pH and salt concentration. Precipitation of proteins occurs when their **solubility decreases**. Unlike denaturation, precipitation is **reversible** and **does NOT** cause permanent loss of protein activity.
- **Salting-in**: Salts at moderate concentration may cause **increased protein solubility**; 5% NaCl is used.
- **Salting out**: Salts at high concentration may **decrease the solubility** resulting in protein **precipitation**. **Ammonium sulphate** is MC used reagent for salting out.
- Other methods of precipitation are:
 - By **heavy metals**: Hg, Zn, Pb etc.
 - By **acids**: phosphotungstic acid, sulphosalicylic acid etc.
 - By **organic solvents**: ether, alcohol, acetone etc.

METHODS OF QUANTATION OF TOTAL PROTEINS

- Kjeldahl's procedure
- Biuret method
- Lowry's method
- Spectrophotometric estimation
- Radial immunodiffusion (Mancini's technique)
- Bradford assay
- Light scattering methods (nephelometry and turbidimetry)
- RIA and ELISA

EXTRA EDGE

- **Bramacrosel Green (BCG)** method is used to estimate total albumin and NOT total protein.
- **Densitometry** is the method to quantitate separated proteins.
- **Zymogen activation** by partial proteolysis is an example of **covalent modification**.
- The MC type of covalent modification is the **reversible protein phosphorylation**.

PROTEIN SEPARATION AND PURIFICATION METHODS

1. Salt fractionation (salting out already described above)
2. Ultracentrifugation
3. Electrophoresis (discussed in detail below)
4. Chromatography (discussed in detail below)

Electrophoresis

- Migration of a charged particle in an electric field is called electrophoresis.
- It is the **MC protein separation method** in the clinical lab.
- Sample is applied at the **cathode** and the analyte moves towards the anode - hence **negatively charged particles move faster**.
- Most **rapid** method of protein separation is **capillary electrophoresis**.
- Types of electrophoresis based on the supporting media used to separate the analyte of interest is given in below table.

Type	Supporting media used	Protein separation principle
Agarose gel electrophoresis	Agarose gel	Based on charge
Polyacrylamide gel electrophoresis (PAGE)	Polymer of acrylamide	Based on charge and molecular weight (size)
SDS PAGE	Sodium Dodecyl Sulphate (SDS) and polyacrylamide	Based on molecular weight (size) only ; used for molecular weight determination
Capillary electrophoresis	Done in capillary tube	Based on charge
Isoelectric focusing	pH gradient is created across the supporting medium by impregnation with ampholyte	Based on isoelectric pH

Chromatography

- This is based on the principle of partition of the proteins between the two phases - **mobile** phase and **stationary** phase.
- Various chromatographic techniques for protein separation are given in below table

Separation principle	Chromatography
Size and shape	Size exclusion (gel filtration) chromatography
Net charge	Ion exchange chromatography
Isoelectric point	Chromatofocusing
Hydrophobicity	Hydrophobic interaction chromatography reversed phase chromatography

Contd...

Contd...

Separation principle	Chromatography
Molecular recognition/ biological function	Affinity chromatography
Metal binding	Immobilized metal ion affinity chromatography
Antigenicity	Immunoabsorption
Carbohydrate content	Lectin affinity chromatography
Content of free -SH	Chemisorption (Covalent chromatography)

High Yield One Liners

- **Most specific** chromatographic technique is **affinity chromatography**.
- **Hydrophobic amino acid moves fastest** along the stationary phase of thin layer paper chromatography (TLPC).
- Amino acid which moves fastest in TLPC is **isoleucine**.
- In TLPC, **nonpolar amino acids** move faster.

STUDY OF PROTEIN STRUCTURE

Determination of Primary Structure/Sequencing of Proteins

- Methods of amino acid sequencing are:
 1. End group analysis
 2. Mass spectrometry
 3. Molecular biology techniques.

End Group Analysis

- Identification of N-terminal and C-terminal amino acid in a polypeptide chain is called end-group analysis.
- Identification of N-terminal amino acid by
 - **Sanger's technique** using Sanger's reagent (1, Fluor, 2,4 DiNitroBenzene, FDNB)
 - **Edman's degradation technique** using Edman reagent (Phenyl isothiocyanate)
- Identification of C-terminal amino acid: using **Carboxypeptidase A and B**

Mass Spectrometry

- **Method of choice for protein identification** and to determine **molecular weight**.
- The molecular mass of each amino acid is unique and hence the sequence of peptides can be reconstructed from the masses of its fragments
- Here, the analyte has to be converted to vapor phase by using various techniques such as
 - **MALDI**: Matrix-assisted Laser Desorption and Ionization

- **FAB:** fast Atom bombardment
- Electrospray ionization
- Heating in vacuum
- Types of mass spectrometers include
 - Tandem mass spectrometry
 - Time of flight mass spectrometer
 - Quadrupole mass spectrometer

Study of Secondary Structure of Proteins

- Circular dichroism
- Optical Rotatory Dispersion Chromatography

Study of Tertiary Structure of Proteins

- X-ray **crystallography** (X-ray diffraction)
- NMR spectroscopy
- Molecular Modeling
- Fluorescence spectroscopy
- UV light spectroscopy and **Infrared spectroscopy**
- **Mass spectrometry**

BLOOR'S CLASSIFICATION OF LIPIDS

Simple Lipids

- **Fats:** *Neutral fats (triglycerides)* are esters of fatty acids + trihydric alcohol glycerol.
- **Oil:** A fat in the liquid state is known as **oil**.
 - **"Visible" fats** are those that are separated from their natural source, e.g. ghee, butter, cooking oils from oil bearing seeds and nuts
 - **"Invisible" fats** are those, which are not visible to the naked eye, e.g. present in pulses, cereals, and nuts.
- **Waxes** are esters of fatty acids + higher molecular weight monohydric alcohols (other than glycerol).
 - They are of the nature of insect secretions, e.g., bee wax, lanoline (ester of cholesterol, used in cosmetic creams), spermaceti (oil from the head of sperm whale used in making candles).

Compound Lipids

- They are esters of fatty acids + alcohols + additional groups (like phosphoric acid, carbohydrates, proteins etc.).
- **Phospholipids:** Fatty acid + alcohol (glycerol/sphingosine) + Nitrogenous base. Phospholipids are divided into
 - **Glycerophospholipids:** (alcohol here is glycerol) - Examples are:
 - **Lecithin - phosphatidyl-choline**; See box below.
 - **Cephalin: phosphatidyl-ethanolamine**, similar to lecithin but the base is ethanolamine instead of choline.

- **Cardiolipin:** is **diphosphatidyl glycerol**, found in membranes of **mitochondria**
- **Plasmalogens:** Similar to cephalin but with an ether link on C1.
- **Sphingophospholipids:** (alcohol here is the amino alcohol sphingosine). Example is
 - **Sphingomyelins:** Contain fatty acids + alcohol (sphingosine) + choline + phosphoric acid.
 - **Ceramide** = Sphingosine + Fatty Acyl CoA
- **Glycolipids or Glycosphingolipids:** Fatty acid + alcohol (sphingosine) + carbohydrate. Examples are:
 - **Cerebrosides:** Are glycolipids containing sphingol, galactose and fatty acid. Present in large amounts in **white matter of brain and in myelin sheaths**.
 - **Gangliosides:** Are glycolipids with **sialic acid**. Present in cell membranes and nerve endings.

Derived Lipids (Precursor Lipids)

- Compounds which are derived from the above groups of lipids. Ex: **fatty acids, cholesterol, glycerol**.

Lecithin

- **Lecithin (phosphatidyl choline):** Contains glycerol, fatty acid, phosphoric acid and choline.
- **Dipalmitoyl lecithin** is **surfactant**.
- Within the HDL particle, the **cholesterol** is esterified by **lecithin-cholesterol acyltransferase (LCAT)**.
- **Familial LCAT deficiency:**
 - **AR**, increased plasma **free cholesterol** level and low plasma levels of cholesterol esters (HDL-C and apoA-I) BUT despite low HDL, **premature atherosclerosis** is NOT a consistent feature of LCAT deficiency
 - Complete deficiency (classic LCAT deficiency)
 - Partial deficiency (**fish-eye** disease).
 - Progressive **corneal opacification**
 - Variable **hypertriglyceridemia**
 - Hemolytic anemia and progressive renal insufficiency (in complete LCAT deficiency).

FATTY ACIDS

- They contain the elements C, H, O. Most naturally occurring fatty acids are straight chain derivatives and have an even number of carbon atoms.
- Length of fatty acids:
 - **Short** chain fatty acids (C2- C6)
 - **Medium** chain fatty acids (C8-C14)
 - **Long** chain fatty acids (>C16)
- **Saturated fatty acid**
 - There is **no double bond** in the hydrocarbon chain.

- It can be represented by the general formula $C_n(H_{2n+1})COOH$, e.g. acetic acid (1 carbon), lauric acid, stearic acid, palmitic acid.
- **Unsaturated fatty acids**
 - It contains one or more double bonds in the hydrocarbon chain.
 - **Monounsaturated fatty acids (MUFA):** Contain single double bond (at 9th position) in their structure, e.g. oleic acid, palmitoleic acid, elaidic acid, nervonic acid.
 - **Polymunsaturated fatty acids (PUFA):** It has two or more double bonds in the hydrocarbon chain, e.g. **linoleic** acid, **arachidonic** acids, docosahexanoic acid (**DHA**) etc.
- **PUFA** are mostly found in vegetable oils and saturated fats mainly in animal fats.
- **Essential fatty acids (EFA)** are those that cannot be synthesized in the body and can be derived from food.
- The **most important EFA is linoleic acid**; others are **arachidonic** acid (meat, eggs), **linolenic** acid (soybean oil), **eicosapentaenoic** acid (fish oil).
- **Prostanoids:** These compounds, derived from eicoso-(20 C) polyenoic fatty acids comprise the **prostanoids** (prostaglandins, prostacyclins, thromboxanes) and **leukotrienes**.
- **Trans Fatty Acids (TFA)** are formed during the **partial hydrogenation of vegetable oils**. TFA are more **atherogenic** than saturated fatty acids. TFA are present in cakes, cookies, **deep fried foods**.

More about Fatty Acids

- Fatty acid present in human milk is **DHA (docosahexaenoic Acid)**.
- Highest amount of **MUFA** is present in **mustard/rapeseed oil**.
- Highest amount of **PUFA** is present in **Safflower oil**; second highest source of PUFA is **sunflower oil**.
- Highest content of **linoleic acid** is in **safflower oil**.
- Highest content of **medium chain fatty acid** is in **coconut oil**.
- Least source of **PUFA** is in **coconut oil**.
- Among EFA's **arachidonic** acid has **maximum carbon atoms = 20**

Omega Classification of Fatty Acids

- | | |
|---------------|---|
| Omega-3 acids | Alpha Linoleic Acid
Eicosapentanoic acid
Cervonic acid (DHA) |
| Omega-6 acids | Linoleic acids
Linolenic acids
Arachidonic acid |
| Omega-9 acids | Oleic acid
Nervonic acid
Elaidic acid |

EXTRA EDGE

- Docosahexanoic Acid (DHA) synthesized in body from **linolenic** acid.
- High concentrations of DHA found in human **retina, brain and sperms**.
- DHA is supplied transplacentally through breast **milk**.
- Low DHA = increased risk of **retinitis pigmentosa**.

Omega-3 Fatty Acids

- Decrease the risk of **CVS** disease
- **Replaces arachidonic acid** in platelet membranes
- **Lowers** production of **thromboxanes** and tendency of platelet aggregation
- **Decreases** serum **triglycerides**
- Significant for **Infant development**
- Lower risk of **ADHD**
- Used for treating **dry eyes**.
- Lower risk of chronic degenerative diseases - cancer, rheumatoid arthritis and Alzheimer's disease.

Purity of Fats

- Fats are characterized and their purity otherwise assessed by the following chemical constants:

Saponification number	A high value indicates that the fat is made up of low molecular weight fatty acids and vice versa.
Iodine number	Since, iodine is taken up by double bonds; a high iodine number indicates a high degree of unsaturation of the fatty acids in the fat.
Acid number	Indicates the degree of rancidity of the given fat.
Reichert-Meliss number	The number of 0.1 N KOH required to neutralize the volatile fatty acids distilled from 5 g of fat.

More High Yield Points

- **Salkowski, Lieberman-Burchard** reactions are for identification of **cholesterol**
- **Coprosterol:** Is the cis-isomer of dihydrocholesterol and is found in **feces**.
- **Ergosterol:** Occurs in plants and yeast and is important as a precursor of **vitamin D**.
- **Hydrogenation:** When vegetable oils are hydrogenated under optimum temperature and pressure in the presence of a catalyst, liquid oils are converted into semi-solid and solid fat.
- **Vanaspati:** Hydrogenated fat is called "Vanaspati".
- Since vanaspati is lacking in fat-soluble vitamins, it is fortified with vitamins A and D to the extent of **2500 IU of vitamin A** and **175 IU of vitamin D** per 100 grams.
- **Rancidity:** Refers to the unpleasant taste and smell of fats and oils imparted by **cyclic hydrocarbons**; rancidity occurs due to **oxidation** or **repeated heating**.

Fatty Acid Breakdown

- **Fatty acid degradation** is the process in which fatty acids are broken down, resulting in release of energy.
- It includes three major steps:
 1. Activation and transport into mitochondria
 2. Beta-oxidation
 3. Electron Transport Chain
- Fatty acids are transported across the outer mitochondrial membrane by **carnitine palmitoyl transferase-1 (CPT-I)**, and then couriered across the inner mitochondrial membrane by **carnitine**.
- Once inside the **mitochondrial matrix**, fatty acyl-carnitine reacts with co-enzyme A to release the fatty acid and produce **acetyl CoA**.
- **CPT-I** is believed to be the **rate limiting step** in fatty acid beta oxidation.
- Once inside the **mitochondrial matrix**, fatty acids undergo **beta-oxidation**. During this process, two-carbon molecules acetyl-CoA are repeatedly cleaved from the fatty acid. Acetyl-CoA can then **enter the TCA cycle**, which produces NADH and FADH. NADH and FADH are subsequently **used in the electron transport chain** to produce ATP, the **energy currency** of the cell.

- Number of ATP produced from **palmitic acid** (16 carbon) = **106 ATPs**.
- Number of ATP produced from **stearic acid** (18 Carbon) = **120 ATPs**.
- The **peroxisomal beta oxidation** handles **very long chain fatty acids (> 20 carbon)** which are poor substrates for mitochondrial beta oxidation. **Zellweger syndrome** is an inborn error of peroxisomal beta oxidation.

LIPID STORAGE DISEASES OR SPHINGOLIPIDOSES

1. They form a group of **lysosomal storage diseases**. **Lysosomes** contain **hydrolytic enzymes** and a specific enzyme is deficient in each disorder. Hence, usually only a single **sphingolipid** (the substrate for the deficient enzyme) accumulates in the involved organs in each disease.
2. The rate of biosynthesis of the accumulating lipid is normal, only **degradation is affected**.
3. The enzyme deficiencies **usually cause death soon after the first months of life** (except adult form of Gaucher's and of Fabry's disease).

Disease	Enzyme defect	Salient features
Fabry's disease (XLR); " FAX "	α -galactosidase	<ul style="list-style-type: none"> • Angiokeratomas, kidney/heart failure, peripheral neuropathy of hands/feet
Gaucher's disease (AR), MC	β -gluco-cerebrosidase	<ul style="list-style-type: none"> • 3 types – adult, infantile, juvenile. • Hepatosplenomegaly, moderate anemia, osteoporosis, aseptic necrosis of femur, bone crises, Erlenmeyer flask deformity of femur. • NO cherry red spot at macula and NO MR • Gaucher's cells: "Crumpled tissue paper" macrophages, strongly PAS positive. • Treatment: <ul style="list-style-type: none"> • Enzyme replacement - mannose terminated recombinant acid beta glucosidase - Imiglucerase alfa; ALSO Velaglucerase alfa (produced in human fibrosarcoma cells) and Taliglucerase alfa (produced in carrot cells). • Oral substrate reduction agents: Miglustat.
Niemann-Pick, AR	Sphingomyelinase ; " No Mon Picks his nose with his sphinger! "	<ul style="list-style-type: none"> • CNS damage, MR (mental retardation), cherry red spot in macula, foam cells in marrow, fatal in early life, hepatosplenomegaly.
Tay-Sach's disease, AR	Hexosaminidase A	<ul style="list-style-type: none"> • CNS damage, MR, cherry red spot in macula, developmental delay, lysosomes with onion skin
Krabbe's, AR	β -galacto-cerebrosidase	<ul style="list-style-type: none"> • Severe MR; total absence of myelin in CNS, globoid bodies in white matter, optic atrophy, fatal in early life
Metachromatic leukodystrophy	Arylsulfatase A	<ul style="list-style-type: none"> • Central and peripheral demyelination with ataxia, dementia, optic atrophy, mental retardation, flaccid paralysis, decerebrate posturing and death; nerves stain yellowish brown with cresyl violet (metachromasia), fatal in first decade

Contd...

Disease	Enzyme defect	Salient features
Tay-Sach's disease	Hexosaminidase A and B	<ul style="list-style-type: none"> • Same as Tay Sach's but progresses rapidly
Gaucher disease, AR	Acid ceramidase	<ul style="list-style-type: none"> • Infantile and Juvenile forms occur; Occasional MR
Wolman disease and Cholesteryl ester storage disease, AR	Acid lipase	<ul style="list-style-type: none"> • Presents in first week of life with failure to thrive, relentless vomiting, abdominal distension, steatorrhea and death usually occurs within 6 months. • Adrenal gland calcification is pathognomonic

Mucopolysaccharidoses

Disease	Deficient enzyme	Clinical findings
Hurler's (Type 1), AR	α -L-Iduronidase	<ul style="list-style-type: none"> • Children may appear normal at birth; features develop between 6-24 months of age. • Enlarged tongue, coarse face, thick skin (gargolism), • Severe mental retardation, short stature, hepatosplenomegaly, cardiac defects, persistent nasal discharge, stiff joints, hydrocephalus, skeletal deformity, Corneal opacity. • Dermatan sulfate and Heperan sulfate in urine.
Hunter's (Type 2), XLR; "Hunter's aim for the 'X'!"	Iduronate sulfatase	<ul style="list-style-type: none"> • Mild Hurler's + aggressive behavior, deafness, NO corneal opacity. ("Hunter has to see clearly, so NO corneal opacity for Hunter!!")

EXTRA EDGE

- **Morquio's disease** and **MPS-1S Scheie** are **NOT** a/w mental retardation

LIPOPROTEINS

- Lipoproteins are composed of triglycerides; cholesterol and phospholipids.
- Electrophoretic mobility: **HDL > VLDL > IDL > LDL > chylomicrons**.

Particle and origin	Functions	Major apo-lipoproteins	Remarks
Chylomicrons (secreted by Intestinal epithelial cells)	Delivers dietary triglycerides to muscle and adipose tissues. Delivers cholesterol from Intestine to liver in form of chylomicron remnants .	Apo B-48 .	Maximum triglyceride content (lipid rich) BUT least dense Largest particle size (75-1200 nm) Excess causes pancreatitis, lipemia retinalis and eruptive xanthomas Electrophoretic mobility: found at origin (least)
VLDL (Very Low Density Lipoproteins) (secreted by liver)	Delivers hepatic triglycerides to muscle and adipose tissues.	Apo B-100	Electrophoretic mobility: pre-beta Excess causes pancreatitis
LDL (Low Density Lipoproteins) (formed by lipoprotein lipase modification of VLDL in peripheral tissues)	Delivers hepatic cholesterol to peripheral tissues .	Apo B-100	Electrophoretic mobility: beta Excess causes atherosclerosis, xanthomas and coronary senilis - " bad cholesterol ". (LDL is Lousy!) LDL is taken up by target cells via receptor-mediated endocytosis . Oxidised LDL is more atherogenic due to accumulation in macrophages
HDL (High Density Lipoproteins) (secreted from both liver and intestine)	Transports cholesterol from peripheral tissues to liver	Apo A-1	Has fastest electrophoretic mobility (alpha) Lowest triglyceride/lipid content and is most dense Smallest particle size (5-12 nm) Cardioprotective and anti-atherogenic - " good " cholesterol (HDL is Healthy!)

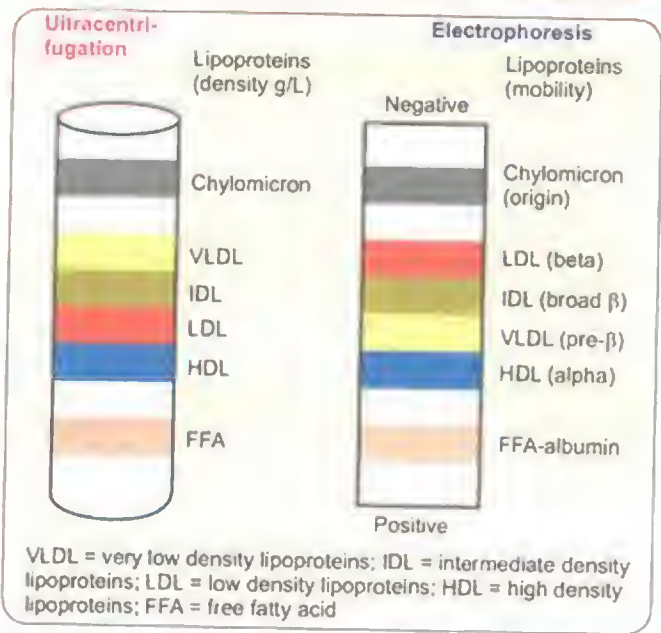


Fig. 4.7: Comparison of electrophoretic and ultra-centrifuge patterns of lipoproteins

APOLIPOPROTEINS

- The proteins associated with lipoproteins, called **apolipoproteins** are required for the assembly, structure, function, and metabolism of lipoproteins.
- Apolipoproteins activate enzymes important in lipoprotein metabolism and act as ligands for cell surface receptors.

Apoprotein	Component of	Functions	Site of production
Apo A1	HDL	Activation of LCAT; major specific ligand for HDL receptor; Anti-atherogenic	Intestine, Liver
Apo AII	HDL	Inhibits LCAT ; stimulates lipase; second major ligand for HDL receptor	Intestine, Liver
Apo B 100	LDL, VLDL	Binds LDL receptor	Liver
Apo B48	Chylomicrons	48% size of B100; major structural apolipoprotein of chylomicrons	Intestine
Apo C1	Chylo, VLDL	Activation of LCAT; anti-atherogenic	Liver
Apo E	LDL, VLDL, Chylomicron	Arginine rich; ligand for hepatic uptake; Apo EIV a/w Alzheimer's disease	Liver
Apo Lp(a)	Lp (a)	Attached to B100; impairs fibrinolysis ; highly atherogenic (leads to acute MI in young age)	Liver

EXTRA EDGE

- Lipoprotein X (LpX): is an index of **cholestasis**.
- IDL** and **LDL** are derived from **VLDL**.
- Triglyceride molecules must be enzymatically digested to **yield monoglyceride and fatty acids**, both of which can **efficiently diffuse or be transported into the enterocyte**
- Hormone sensitive lipase (cholesterol ester hydrolase)** - it mobilises fatty acids from triacylglycerol stores in adipose tissue - "**fat burning enzyme**". It is **activated by** glucagon, ACTH, epinephrine and vasopressin. It is inhibited by **PGE**.

FRICKSON CLASSIFICATION OF HYPERLIPIDEMIAS

Type	Nomenclature	Protein (gene) defect	Lipoprotein elevated	Inheritance
I	Familial Chylomicronemia syndrome	Lipoprotein Lipase or Apo-C2 deficiency	Chylomicrons	AR
IIa	Familial hypercholesterolemia	LDL receptor defect (LDLR)	LDL	AD
IIb	Familial AD hypercholesterolemia type II	Apo-B100	LDL	AD
III	Familial AD hypercholesterolemia type III	PC5 K9	LDL	AD
IV	AR hypercholesterolemia	LDL receptor adapter protein (LDLRAP)	LDL	AR
V	Sitosterolemia	ABCG5 or ABCH8	LDL	AR
VI	Familial combined hyperlipidemia		LDL and VLDL	AR
VII	Familial dysbeta-lipoproteinemia	Apo-E	Chylomicron and VLDL remnants	AR
VIII	Familial hyper-triglyceridemia	Apo-A5	VLDL	AR
IX	Familial hyper-triglyceridemia	Apo-A5 and GP1HBP1	Chylomicrons and VLDL	AR

EXTRA EDGE

- Fish oil** is CONTRAindicated in patients with **type IIa hyperlipoproteinaemia** because of the increase in LDL that it causes.
- Fish oil is rich in omega-3-PUFA and is used to lower plasma triglycerides and hence used to **treat familial hypertriglyceridemia**.

Tangier's Disease

- Also called familial HDL deficiency; Autosomal Co-dominant.
- Severe deficiency of HDL cholesterol (HDL-C)** concentrations in plasma and deposition of **cholesterol esters in various tissues**.
- Mutations in gene encoding adenosine triphosphate binding cassette-1 (**ABCA1**) on chromosome 9q31.
- Classical signs: **Hyperplastic orange yellow tonsils**, **splenomegaly** and **relapsing peripheral neuropathy**.
- Other signs: **Hepatomegaly**, **abnormal rectal mucosa**, **corneal opacity**, **anemia**, **lymphadenopathy**, **thrombocytopenia**, **premature coronary heart disease**.

CHEMISTRY OF CARBOHYDRATES

- The general formula $C_n(H_2O)_n$ represents most of the carbohydrates.
- In general 2^n gives the number of optical isomers possible for given sugar, where 'n' stands for the number of **asymmetric carbon atoms** in the molecule - **Lebel can't Hoff's rule**.
- Carbohydrates** can be **defined as aldehyde or ketone derivatives of polyhydroxy alcohols**.

Monosaccharides

- Monosaccharides are sugars which **cannot** be further hydrolyzed.
- They are compounds with **2-10 carbons** per molecule.
- They are the **building blocks** of all carbohydrates. Monosaccharides may be **aldoses** (with aldehyde group) or **ketoses** (with keto group).
- Important monosaccharides are given in below table

No. of C atoms	Name	Aldose	Ketose
3	Triose	Glyceraldehyde	Dihydroxyacetone
4	Tetrose	Erythrose	Erythrulose
5	Pentose	Ribose Xylose	Ribulose Xylulose
6	Hexose	Glucose, Galactose, mannose	Fructose
7	Heptose		Sedoheptulose

EXTRA EDGE

- Sialic acids**: N-Acetyl **neuraminic acid** (which is a **nanose**). It is a component of glycoprotein and ganglioside.

Biologically Significant Hexoses

- D-glucose**:
 - The **carbohydrate currency** of the body.
 - Most **predominant sugar** in the body
 - Universal fuel of fetus
 - Glucose is **dextrorotatory** - hence also called **dextrose**.

➤ Organs whose *major energy source* is glucose is: **Brain, RBC (in both in fed and starving state), Cornea, Retina, Renal medulla and testes.**

- **D-fructose:** Present in *fruit juices, honey* and *seminal fluid*.
- **D-galactose:** Constituent of *lactose* or 'milk sugar'.
- **D-mannose:** Constituent of several *glycoproteins* and plant-derived *gums*.
- All hexoses have a free functional group, hence they are reducing sugars.

Disaccharides

- General formula: $C_n(H_2O)_{n-1}$
- These are formed by union of *two monosaccharides* held together by *glycosidic bonds*.

Reducing disaccharides - Free Functional Group present

Maltose	Consists of two α-D-glucose units (α1-4 linkage).
Lactose	Consists of a molecule of α-D-glucose and a molecule of β-D-galactose (β1, 4-linkage).
Lactulose	Galactose + Fructose (α1-β4 linkage)

Non-reducing disaccharides - No Free Functional Group

Sucrose	α-D-glucose + β-D-fructose united by a glycosidic linkage between the aldehyde and keto groups (C1 of glucose and C2 of fructose; α1-β2 linkage); sucrose also called <i>“invert sugar/cane sugar”</i>
Trehalose	Glucose + Glucose; sugar of insect hemolymph; yeast and fungi

Oligosaccharides

- These are made up of **3-10 molecules of monosaccharides** joined together by glycosidic bond.
- Blood group substances are oligosaccharides.

Polysaccharides

- These are made up more than **10 molecules of monosaccharides**.

Homo-polysaccharides (Homo-glycans)	Hetero-polysaccharides (Hetero-glycans)
Contain only one type of monosaccharide	Contain different types of monosaccharide
Polysaccharides of glucose (glucosan): Glycogen	Glycosaminoglycans (mucopolysaccharides):
• Starch	• Hyaluronic acid
• Cellulose	• Chondroitin sulfate
• Chitin	• Keratan sulfate;

Contd...

Contd...

Homo-polysaccharides (Homo-glycans)	Hetero-polysaccharides (Hetero-glycans)
• Dextran	• Heparin
• Dextrin	• heparan sulfate
Polysaccharides of fructose (fructosan):	• Dermatan sulfate
• Inulin	• Agar
	• Agarose
	• Pectin

More about Individual Polysaccharides

- **Starch:** Made up of two polysaccharides: *Amylose* and *amylopectin*.
- **Amylose:** polymer of 200-1000 α-D-glucose molecules (1-4 linkage), soluble in hot water, gives *blue color with iodine*.
- **Amylopectin:** Polymer of hundreds of chains of α-D-glucose molecules united by 1-4 linkages *like branches of a tree* attached to neighboring chain by 1-6 linkage, forms a gel with hot water and gives a *violet color with iodine*.
- **Glycogen:** Also known as *animal starch*.
- **Cellulose:** **Most abundant carbohydrate in nature** (chief constituent of plant cell walls), consists of long chains of β-D-glucose molecules united by 1-4 linkages; insoluble; major component of dietary fibre; humans lack enzymes that hydrolyse beta 1-4 glycosidic bonds
- **Inulin:** *Low molecular weight polysaccharide* (MW 5000), consisting of *d-fructose units*, occurs in *tubers of onion, garlic, dahlia, and chicory*; Used to estimate **GFR**.
- **Agar:** Present in *seaweeds* consists of sulfated galactose units. It dissolves in hot water and sets to a gel on cooling.
- **Pectins:** present in *apple, lemon and other fruits*. They are polysaccharides of galacturonic acid, galactose and the pentose sugar arabinose.
- **Chitin:** Present in *exoskeleton of invertebrates* like crustaceans (crab, lobster) and insects.
- **Dextran:** *Plasma volume expander; others are human albumin, hydroxy ethyl starch*
- Major constituent of bacterial cell wall are heteropolysaccharid, consisting of repeating units of N-acetyl muramic acid (NAM) and N-acetyl glucosamine (NAG).

Glycosaminoglycans (Mucopolysaccharides)

- **Glycosaminoglycans** - GAGs or **Mucopolysaccharides** are heteropolysaccharides containing **uronic acid + amino sugars**.

- **Heparin:** is a **sulfated GAG anticoagulant** and is isolated from mammalian tissues rich in **mast cells**. Most commercial heparin is derived from **porcine intestinal mucosa** and is a polymer of alternating **D-glucuronic acid** and **N-acetyl-D-glucosamine** residues
- **Chondroitin sulfate:** **Most abundant GAG**; a major component of **cartilage**.
- Combination of **glucosamine + chondroitin sulfate** is used in the treatment of **osteoarthritis**.
- **Hyaluronic acid:** Present in connective tissue; **viscous humor, tendons, synovial fluid** (lubricant in joint cavities). Also found in **bacteria**. **Mucin clot test (rope test)** is to detect hyaluronate in synovial fluid.
- **Keratan sulfate:** only GAG with NO uronic acid.

Glycoproteins and Mucoproteins

- Carbohydrates (**Polysaccharides**) + polypeptide chains = **Proteoglycan**.
- If carbohydrate content < 10%, it is called **glycoprotein** and if > 10% it is called **mucoprotein**.

More about Glucose

- Glucose contains **six carbon** atoms, one of which is part of a sugar group, and is therefore referred to as an **aldohexose**. (*Fructose* is a **ketohexose**).
- In solution, the glucose molecule can exist in an open chain (acyclic) form and a ring (cyclic) form (in equilibrium). The cyclic form is the result of a **covalent bond between the aldehyde C atom (CHO) and the C-5 hydroxyl (OH) group** to form a six- membered cyclic **hemiacetal**.
- **Epimers:** **2 sugars**, which differ from one another only in the configuration around one specific carbon atom, are called '**epimers**' of each other, e.g. D-galactose and D-mannose with respect to C-2.
- **Mutarotation:** is explained by the existence of two optical isomers of glucose, α-D-glucose with a specific rotation of +112° and β-D-glucose with a specific rotation of +19°.
- **Ring structures of glucose:** '**pyranose**' (Haworth), A 6 membered ring; '**furanose**' a 4 membered ring. This ring structure may be in the form of a '**chair**' (more stable) or a '**boat**'.
- **Saccharic acids:** Nitric acid oxidises the aldehyde group as well as the primary alcoholic group of glucose to produce saccharic acids.
- **Inversion:** The phenomenon by which the **dextrorotatory sucrose is converted to levorotatory mixture of glucose and fructose**.

Polyol Pathway of Glucose

- Glucose is **reduced** by aldose reductase to form **sorbitol**; sorbitol is then be oxidized to fructose.
Glucose → sorbitol → fructose.
- **Glucose when converted to sorbitol**, cannot diffuse out of the cell easily and gets trapped there. Sorbitol is normally present in the lens of the eye. But in **diabetes mellitus, when glucose levels are high, the sorbitol concentration also increases in the lens**. This leads to osmotic damage of the tissue and the development of cataract.

Isomers

- Isomers are compounds, which have the same elemental composition and same empirical formula, but different molecular structure.
 - **Structural isomerism**—e.g. Dimethyl ether and ethyl alcohol
 - **Geometrical isomerism**—Depending on the position of the H⁺ and COOH groups, there are Cis- and Trans- isomers, e.g. Maleic acid ("Cis") and fumaric acid ("Trans").
 - **Optical isomerism**—D-lactic acid and L-lactic acid.
- **Racemic mixture:** Equimolar mixture of optical isomers which has no net rotation of plane of polarised light.
- **Enantiomers:** Difference in the orientation of H and OH group around penultimate carbon atom results in two mirror images called D and L isomers
- **Anomers:** The α and β forms of glucose are called '**anomers**' and **C-1** the anomeric carbon atom.
- **Epimers:** Difference in the orientation of H and OH group around carbon atoms other than anomeric carbon and penultimate carbon results in isomerism referred to as Epimerism.
 - 2nd epimer of glucose (at C2): Mannose
 - 3rd epimer of glucose (at C3): Allose
 - 4th epimer of glucose (at C4): Galactose.

Tests for Carbohydrates

Test	Purpose
Molisch test	General test for all CHO
Benedicts test	Test for reducing substances
Barfoed's test	Test to differentiate Monosaccharides and disaccharides
Moore's test	
Fehling's test	
Seliwanoff's test	Test to differentiate aldoses and ketoses
Foulger's test	
Rapid furfural test	

Contd

Contd

Test	Purpose
Feulgen staining	Test to detect deoxy sugar
Bial's test	Test for pentoses
Mucic acid test	Test for Galactose

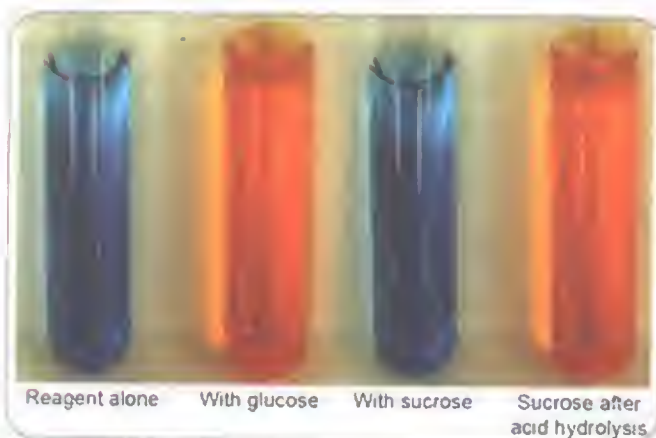


Fig. 4.8: Benedict's test is positive for glucose. Test is negative for sucrose; but when sucrose is hydrolyzed, the test becomes positive (specific sucrose test)

Methods for Estimation of Glucose

- **Reductometric Methods**
 - Nelson-somogyi method
 - Folin wu method
 - O-toluidine method
- **Enzymatic Method**
 - Hexokinase method (better)
 - Glucose oxidase-peroxidase method
 - Glucose dehydrogenase method
- **Enzymatic methods** are used in automated chemistry analysers and **glucometers**.

Absorption of Carbohydrates

- By two sets of transporters
 - Sodium Dependent Glucose Transporters (**SGLT**)
 - Sodium independent Glucose Transporters (**GLUTs**)

SGLT	GLUT
Secondary Active transport Unidirectional SGLT is coupled with Na^+/K^+ -ATPase pump SGLT-1 is present in Intestine . SGLT-2 is present in renal tubules Phlorizin inhibits SGLT2>SGLT1	Passive process down the concentration gradient Bidirectional Facilitative diffusion Ping-Pong mechanism Phloretin inhibitor of GLUT-1 or GLUT-4.

Summary of Glucose Transporters

Transporter	Present in	Properties
GLUT1	RBC , Brain, Kidney, colon, retina , placenta	Glucose uptake in most of cells
GLUT2	Serosal surface of intestinal cells, liver, beta cells of pancreas	Low affinity; glucose uptake in liver; glucose uptake in beta cells
GLUT3	Neurons, Brain	High affinity; glucose into brain cells
GLUT4	Skeletal and heart muscle; adipose tissue	Insulin mediated glucose uptake
GLUT5	Small intestine, testis, sperms kidney	Fructose transporter; poor ability to transport glucose
GLUT7	Liver endoplasmic reticulum	glucose from ER to cytoplasm

Disorders of Galactose and Lactose Metabolism

Classic Galactosemia	<ul style="list-style-type: none"> • Deficiency of galactase-1-phosphate uridylyltransferase. • AR, Damage is caused by accumulation of toxic substances (Including galactitol / dulcitol). • Symptoms: cataracts (all drop), hepatosplenomegaly, mental retardation. • Treatment: exclude galactose and lactose (galactose + glucose) from diet
Galactose epimerase deficiency	<ul style="list-style-type: none"> • Similar to above + hypatania and nerve deafness
Galactokinase deficiency	<ul style="list-style-type: none"> • Causes galactosemia and galactosuria, galactitol accumulation (cataracts) if galactose is present in diet.
Lactase deficiency	<ul style="list-style-type: none"> • Age-dependent and/or hereditary lactose intolerance (blacks, Asians) due to loss of brush-border enzyme. • Symptoms: bloating, cramps, osmotic diarrhea. • Treatment: AVOID MILK or add lactase pills to diet.

Disorders of Fructose Metabolism

Disease	Enzyme defect	Clinically
Essential fructosuria	Fructokinase	<i>Asymptomatic</i> , positive urine reducing substance; Benign condition
Hereditary fructose intolerance	Fructose 1-phosphate aldolase B	Vomiting, lethargy, failure to thrive, hepatic failure; Prognosis good with early diagnosis and fructose restriction
Fructose 1,6-diphosphatase deficiency	Fructose 1,6-diphosphatase	Episodic hypoglycemia and lactic acidosis; AVOID fasting, good prognosis

SITES OF METABOLIC PROCESSES

Mitochondria	<ul style="list-style-type: none"> • TCA (Kreb's, Citric acid) cycle, • β Fatty acid oxidation • Electron transport chain (oxidative phosphorylation) • Pyruvate to oxaloacetate (Acetyl CoA production)
Cytoplasm	<ul style="list-style-type: none"> • Glycolysis (Embden-Meyerhof pathway), • Pentose phosphate pathway (HMP shunt), • Fatty acid synthesis • Cholesterol (steroid) synthesis
Both (Mitochondria and cytoplasm)	<ul style="list-style-type: none"> • Heme synthesis • Urea synthesis • Gluconeogenesis • "HUG needs Both!"

RATE-LIMITING ENZYMES OF METABOLIC PROCESSES

Process	Enzyme
Glycogenesis	Glycogen synthetase
Glycogenolysis	Phosphorylase
Glycolysis	Phosphofructokinase-1 (PFK-1)
Gluconeogenesis	Phosphoenolpyruvate carboxykinase,
Fatty acid synthesis	Acetyl-CoA carboxylase
Cholesterol synthesis	HMG-CoA reductase
Bile acid synthesis	7- α -hydroxylase
Urea synthesis	Carbamoyl phosphate synthetase-1
Porphyrin synthesis	δ -aminolevulinatase synthetase
Drug metabolism	Xanthine oxidase

Contd...

Contd...

Process	Enzyme
Purine biosynthesis	Phosphoribosyl pyrophosphate synthetase
HMP shunt	Glucose-6-Phosphate dehydrogenase
TCA cycle	Isocitrate dehydrogenase

GLYCOLYSIS (EMBDEN-MEYERHOF PATHWAY)

Characteristics of Glycolysis

- Major pathway of glucose utilization
- **ONLY** pathway taking place in **all cells of the body**
- **ONLY** pathway which can operate **aerobically and anaerobically**
- **ONLY** source of energy for **mature RBC**
- Major source of energy for **skeletal muscle**
- **Metabolism of cancer cells** is also by glycolysis.

- Glycolysis is the **oxidation of glucose to pyruvate with production of ATP** in muscle, fat and non-gluconeogenic tissue. The pathway also metabolizes glucose derived from glycogen, galactose and fructose.
- Occurs in the **cytoplasm**.
- **Anaerobic glycolysis:** Glycolysis also occurs in the absence of oxygen (i.e. anaerobic), when **pyruvate is converted to lactate**.
- **Number of ATP produced** per mole of glucose:
 - In **aerobic glycolysis** = 7.
 - In **anaerobic glycolysis** = 2.
- Glycolysis in RBCs **even** under aerobic conditions always terminates in lactate, because mitochondria that contain the enzymatic machinery for the aerobic oxidation of pyruvate are absent!
- **Please note the irreversible steps of glycolysis** mentioned in the attached figure (in red); (memory aid - all kinases are irreversible except 1,3 Bi-phosphoglycerate kinase which is reversible)
- **Substrate level phosphorylation** in Glycolysis:
 - Phospho glycerate kinase (1,3 bi-phosphoglycerate to 3 phosphoglycerate)
 - Pyruvate kinase (Phosphoenol pyruvate to pyruvate)

Inhibitors of glycolysis

- Iodoacetate
- Fluoride
- Enolase

Pyruvate Kinase Deficiency

- As mentioned above, RBCs metabolize glucose **anaerobically** (NO mitochondria) and thus **depend solely on glycolysis**.

- In genetic pyruvate kinase deficiency (AD, AR), reduced activity of $\text{Na}^+\text{-K}^+$ ATPase leads to **RBC swelling and lysis - leads to hemolytic anemia**.

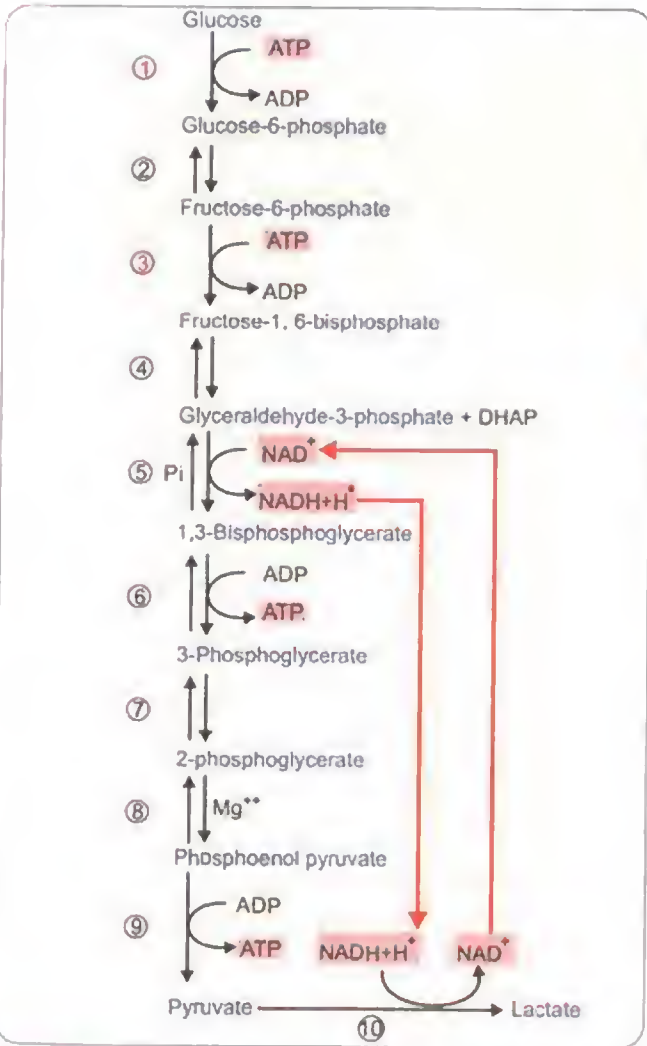


Fig. 4.9: Summary of glycolysis (Embden-Meyerhof - Parnas pathway). Steps 1, 3 and 9 are key enzymes; these reactions are irreversible. Steps 6 and 9 produce energy. Steps 5 and 10 are coupled for regeneration of NAD^+ .

EXTRA EDGE

- Pasteur effect:** The inhibitory effect of oxygen on glycolysis is called Pasteur effect.
- Warburg hypothesis:** Cancer cells use energy from **aerobic glycolysis** and they require less energy than their normal counterparts. **FDG PET** uses this glucose hunger of cancer cells to detect rapidly proliferating tumor cells.

Comparison of Hexokinase and Glucokinase

	Hexokinase	Glucokinase
Occurrence	In all tissues	Only in Liver
Km value	10^{-3} mmol/L	20 mmol/L
Affinity to substrate	High	Low
Specificity	Acts on glucose, fructose and mannose	Acts only on glucose
Induction	Not induced	Induced by insulin and glucose
Function	Even when blood sugar level is low, glucose is utilized by body cells	Acts only when blood glucose level is > 100 mg/dL; then glucose is taken up by the liver cells for glycogen synthesis

GLUCONEOGENESIS

Substrates for gluconeogenesis include

- Glucogenic amino acids** (alanine, glutamic acid, aspartic acid, etc.) - through TCA cycle (**alpha ketoglutarate** also through TCA cycle).
- Any of the intermediates of glycolysis or the TCA cycle e.g. **pyruvate, oxalacetate, lactate and fructose**
- Glycerol**
- Propionyl CoA**

- Gluconeogenesis** is the synthesis of **glucose from non-glucose precursors**.
- Sites: **Liver, kidney or intestinal epithelium**, NOT in muscle
- Occurs in the **cytoplasm**.
- Most steps in gluconeogenesis are the reverse of those found in glycolysis; **three unique enzymic steps** are **glucose-6-phosphatase, fructose-1,6-bisphosphatase, and PEP carboxykinase**.
- The **net result** of the conversion of pyruvate to glucose is the consumption of 6 moles of ATP and 2 moles of NADH .
- All citric acid cycle intermediates can be used for gluconeogenesis.
- Gluconeogenesis is inhibited by insulin** by repressing the key enzymes **pyruvate carboxylase, phosphoenolpyruvate kinase and glucose-6-phosphatase**.

Functions of Gluconeogenesis

- Important during **starvation and interdigestive periods** (especially at night) to maintain steady blood glucose for brain cell metabolism. During fasting, protein is the most important glucose source.
- During severe exercise**, gluconeogenesis allows the use of lactate from anaerobic glycolysis and of glycerol from fat breakdown.
- Allows the use of dietary protein in carbohydrate pathways after disposing of the amino acid nitrogen as urea.

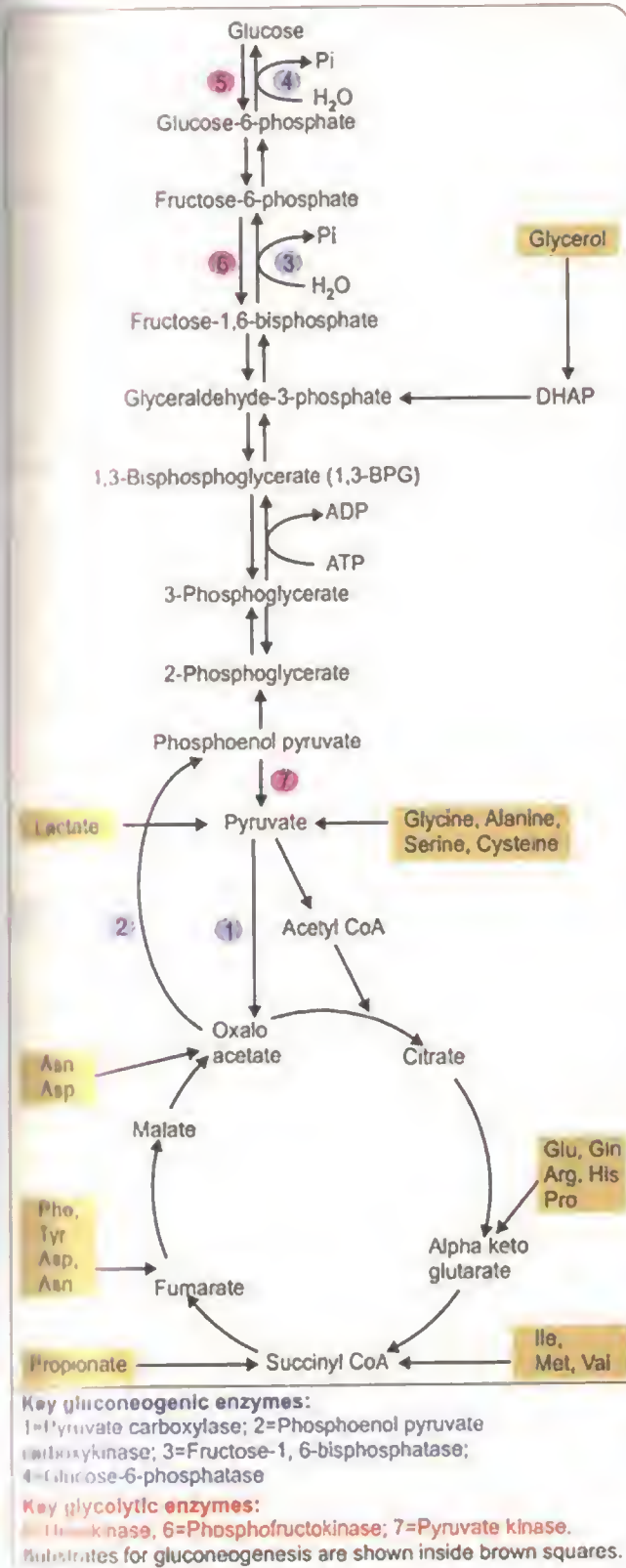


Fig. 4.10: Gluconeogenic pathway

Cori Cycle (Lactic Acid Cycle)

- Coric cycle involves **Liver, muscle and blood**.
- During **strenuous muscular activity**, **glycogenolysis is stimulated** and the resulting glucose-6-phosphate (G-6-P) is further metabolized by the glycolysis and then by oxidation within the TCA cycle to supply the necessary energy.
- When the rate of glycolysis exceeds the availability of oxygen, glucose is converted to lactate in the muscle by **anaerobic glycolysis**.
- The **Cori cycle allows this lactate to undergo hepatic gluconeogenesis and become a source of glucose for muscles/RBCs**. This comes at a cost of net loss of 4 ATP/cycle. Therefore, this cycle **CANNOT** be sustained indefinitely. Hence lactate buildup in muscle may lead to **fatigue**.

Pentose Phosphate Pathway or Hexose Monophosphate (HMP) Shunt

- Occurs in the **cytoplasm**.
- Sites: **Muscle, liver, fat cells, thyroid, lactating mammary gland and erythrocytes**.
- NO ATP is used or produced!**
- Consists of two branches, an oxidative and non-oxidative branch.

Reactions	Key enzymes	Products	Functions
Oxidative (irreversible)	Glucose-6-phosphate-dehydrogenase (G6PD)	NADPH	For fatty acid steroid synthesis Maintenance of glutathione in a reduced form inside erythrocytes
Nonoxidative (reversible)	Transketolases (requires thiamine, Vit. B1)	Ribose-5-phosphate	For nucleotide and nucleic acid synthesis

G6PD Deficiency

- Maintenance of integrity of RBC membrane is as follows:
- HMP pathway** - Production of NADPH , which maintains glutathione in reduced state - this in turn detoxifies free radicals and peroxides.
 - Glycolysis** - to produce 2ATP, which maintains Na^+ and K^+ distribution across the cell membrane.
 - In **G6PD deficiency** $\rightarrow \downarrow \text{NADPH} \rightarrow$ poor defense against oxidizing agents \rightarrow RBC lysis \rightarrow hemolytic anemia.
 - Precipitating factors in G6PD deficiency:** Infection (**MC cause**); oxidant drugs (antibiotics, antimalarials,

amipyretics, antituberculous); favism (ingestion of fava beans); neonatal jaundice; ingestion of *naphthalene camphor ball (mothballs)*

Glycogen and Glycogen Metabolism

- Glycogen is a α 1,4 glucose polymer with α 1,6 branches. It is the storage form of glucose, and is found in abundance in the liver, kidney and muscle.
- Liver glycogen can be mobilized for the release of glucose to the rest of the body, but muscle glycogen can *only be used to support muscle glycolysis*.
- In an average 70 kg man:
 - Liver glycogen = 70 g
 - muscle glycogen = 245 g

Glycogenesis	Glycogenolysis
<ul style="list-style-type: none">Conversion of excess glucose to glycogen for storagePromoted by glycogen synthetaseActivated by insulin	<ul style="list-style-type: none">Degradation of stored glycogenPromoted by phosphorylaseActivated by glucagons, adrenaline
<ul style="list-style-type: none">Inhibited by adrenaline, glucagons	<ul style="list-style-type: none">Inhibited by insulin

Glycogen Storage Disease

Disease	Enzyme-deficient	Comments
Disorders with hepatomegaly and hypoglycemia		
Von Gierke's (Type 1)	Glucose-6-phosphatase	Hepatomegaly and severe fasting hypoglycemia; hyperuricemia, lactic acidosis; hyperlipidemia
Cori's, Forbes - Limit dextrinosis (Type 3)	Amyloglucosidase (Debranching enzyme)	Hepatomegaly and hypoglycemia
Her's (Type 6)	Liver phosphorylase	
Disorders with muscle-energy impairment		
McArdle's (Type 5) <i>M's</i>	Muscle glycogen phosphorylase	Muscle cramps, Myoglobinuria, Male preponderance, exercise intolerance; compensated haemolysis in Tarui's
Tarui's (Type 7)	Phosphofructokinase	
Disorders with skeletal and cardiac muscle impairment		
Pompe's (type 2) (Pumpe's = "pump" failure)	Acid α glucosidase (Acid maltase)	Skeletal muscle weakness, severe cardiomegaly and failure
Disorders with liver cirrhosis		
Anderson's - amylopectinosis	Amylo-transglucosidase	Failure to thrive, hepatomegaly, progressive liver cirrhosis and failure (usually death before 5 th year)

EXTRA EDGE

- Enzyme common to glycogenesis and glycogenolysis is **phosphoglucomutase**.
- Glucose 6 phosphatase** is absent in muscle.

Fate of Pyruvate

- Pyruvate** is an intermediary product of glucose metabolism in the cytoplasm, which links together glycolysis, the TCA cycle, amino acid metabolism and fatty acid oxidation.
- It crosses the mitochondrial membrane and may:
 - React with **coenzyme A** to produce **acetyl-CoA** and NADH (pyruvate dehydrogenase), which can then enter the TCA cycle or lipid metabolism.
 - Condense with CO_2 to form **oxaloacetate** (pyruvate carboxylase).
 - Form **alanine** (transamination).
 - Be **reconverted to glucose** (gluconeogenesis).
 - Be **reduced to lactate** in the absence of oxygen (lactate dehydrogenase), with net synthesis of two molecules of ATP per molecule of glucose.

EXTRA EDGE

- In **Type 1b Glycogen Storage Disease**, **translocase** that transports glucose-6-phosphate across the microsomal membrane is defective.

Electron Transport Chain and Oxidative Phosphorylation

- It is the **final stage in the oxidation of glucose, fatty acids and amino acids**.
- Occurs in the **mitochondria**.
- Formation of ATP from ADP and inorganic phosphate (Pi) while electrons (hydrogen ions) are transferred through a series of sequential oxidation-reduction reactions by enzymes of the electron transport chain. (NAD) linked dehydrogenases, flavoproteins and cytochromes in the mitochondria). These two processes of electron transport and phosphorylation are said to be **coupled**.
- When electron transport proceeds without concomitant ATP production, the reactions are said to be **uncoupled**; **2,4 dinitrophenol is a classic uncoupler**.
- The net result** is the transfer of electrons from NADH and FADH2 to oxygen, forming water.
- Cytoplasmic reducing equivalents, NADH and FADH2 are transported into the mitochondria by the **glycerol phosphate shuttle and the malate-aspartate shuttle**.
- Main function** is to regulate the NADH/NAD⁺ and ATP/ADP for the activation or inhibition of pathways of the cell according to requirements.
- 1 NADH - 2.5 ATP; 1 FADH2 - 1.5 ATP

- Electron carriers** in the electron transport chain are:
 - Coenzyme
 - Cytochrome C
 - Fe-S (Iron-sulphur) centres
 - Heme

Inhibitors of the Electron Transport Chain

Inhibitor	Site
Rotenone	NADH-Ubiquinone reductase (Complex I, one)
Barbiturates	
Antimycin A	Ubiquinol Cyt C reductase (Complex III)
Cyanide, H2S	Cytochrome oxidase (Complex IV)
Carbon monoxide	
Azide	
Oligomycin	ADP phosphorylation (ATP synthase inhibitor)
Atractyloside and bongkrekate	ADP-ATP transporter

High Energy Phosphate Compounds

- Compounds which on hydrolysis result in the transfer of a large quantity of energy.
- Most important is ATP**. On hydrolysis to ADP it liberates energy directly to processes as muscle contraction, active transport and the synthesis of many chemical compounds.
- Other high-energy phosphate compounds include **creatine phosphate**, **guanosine triphosphate (GTP)**, **uridine phosphate (UTP)**, and **cytidine triphosphate (CTP)**.

Tricarboxylic Acid (TCA) Cycle/Citric Acid Cycle/Kreb's Cycle

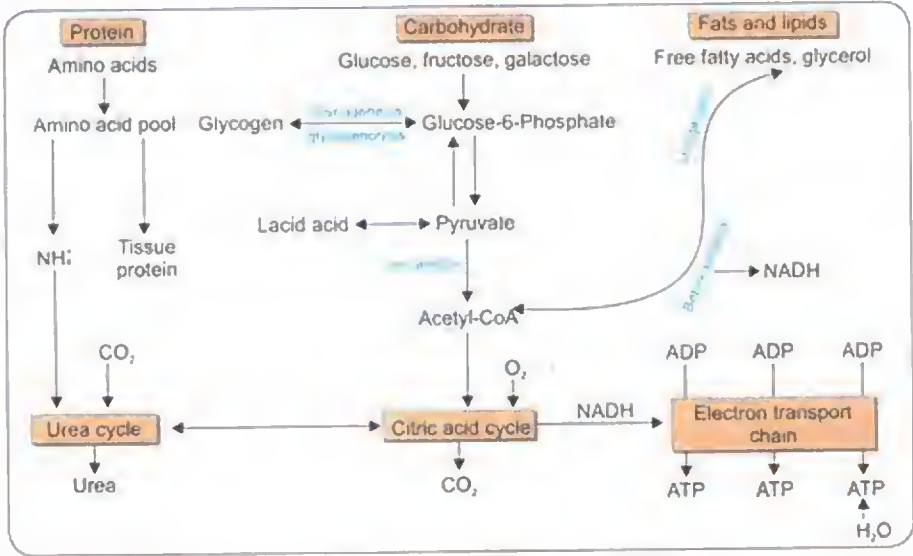


Fig 1.11: Final metabolic pathway summary

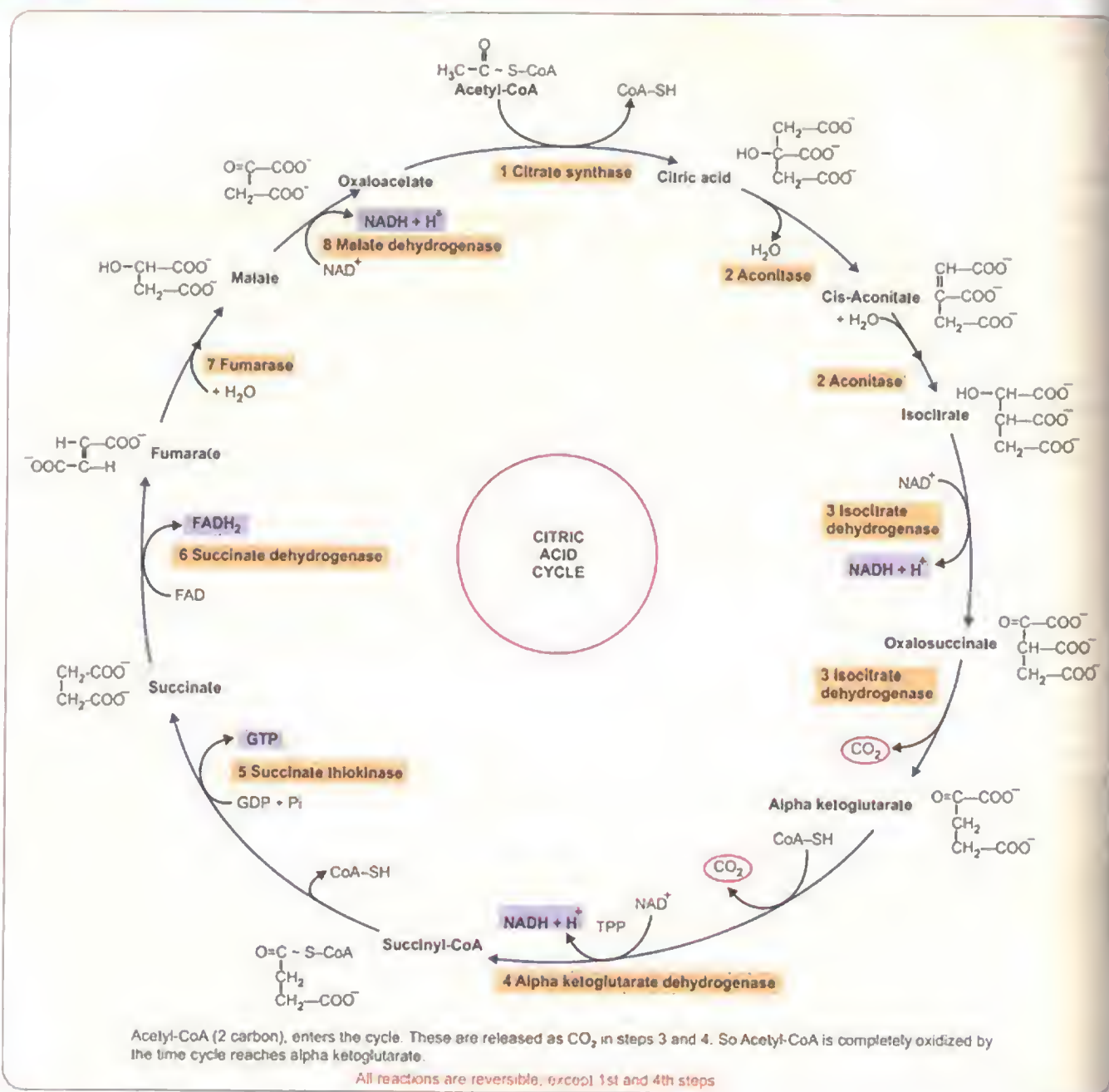


Fig. 4.12: Krebs cycle or citric acid cycle or tricarboxylic acid cycle

- **Final common pathway** for the oxidation of carbohydrate, fat and some amino acids to CO₂ and H₂O
- Occurs in the **mitochondria**
- Occurs in any kind of cell **Except** mature RBC
- **ONLY** active under **AEROBIC** conditions.
- It is an **amphibolic pathway**, i.e. it is involved in both anabolic and catabolic processes.
- Some of the cycle components serve as entry or exit points for other pathways, e.g. gluconeogenesis, transamination, deamination and lipo-genesis.
- Hans **Krebs** received the **Noble Prize** in Physiology in 1953 for his discovery of the TCA in 1937. (See above Fig. 4.12)

What We Understand from the above Diagram is:

- **Oxaloacetate and acetyl-CoA** condense to form **citrate**.
- Citrate is then converted to oxaloacetate by a series of **nine reactions**.
- 3 molecules of NADH (=3X2.5 = 7.5 ATP) and one molecule of FADH₂ (= 1.5 ATP) are produced for each molecule of acetyl CoA catabolised in one turn of the cycle. (7.5 + 1.5 = 9 ATP); 2 CO₂ are also produced.
- **Succinyl CoA** is converted to succinate by the enzyme **succinate thiokinase (succinyl coA synthetase)** - example of **substrate level phosphorylation** (= 1 GTP= 1 ATP).
- Thus in each TCA cycle, **10 ATP is produced for each molecule of acetyl-CoA** catabolised in one turn of the cycle. Remember! 2 acetylCoA are produced from one glucose molecule.
- **Fluoroacetate** inhibits **aconitase** and **arsenite** inhibits **alpha ketoglutarate dehydrogenase** (both non-competitively); **malonate** inhibits **succinate dehydrogenase** (competitively).

EXTRA EDGE

- **Mnemonic:** to remember the 9 reactions of Krebs Cycle in order - "Citrate Is Krebs's Starting Substrate For Making Oxaloacetate" = "Citrate Isocitrate Ketoglutarate Succinyl CoA Succinate Fumarate Malate Oxaloacetate"
- The major **anaplerotic (filling up) reaction** is pyruvate to oxaloacetate by **pyruvate carboxylase**.
- **Oxaloacetate** maybe considered as a "**true catalyst**" which enters and leaves the cycle unchanged!

Vitamins in the TCA cycle

- **Riboflavin** in the form of flavin adenine dinucleotide (FAD)
- **Niacin** in the form of nicotinamide adenine dinucleotide
- **Thiamine** (B₁) as thiamin diphosphate
- **Pantothenic acid** as part of coenzyme A.

Energy Yield from 1 mol of Glucose

- From aerobic glycolysis = 7 ATPs
- From pyruvate dehydrogenase (2 pyruvates form 1 mol of glucose) 2 NADHs = 5 ATPs
- From TCA cycle (2 Acetyl CoA from 1 mol of glucose) 2 X 10 = 20 ATPs
- Therefore, **complete oxidation of one molecule of glucose** to CO₂ and H₂O produces **32 ATP** (7 +5 + 20-) (in aerobic conditions).

The **coenzymes needed for pyruvate dehydrogenase complex** are:

- Coenzyme A (Co-A)
- Thiamine pyrophosphate (TPP)
- FAD
- NAD⁺

HEMOGLOBIN

Hemoglobin Structure

- Each hemoglobin molecule consists of **a globin molecule and 4 haem groups (tetramer - conjugated protein)**.
- **Haem part:** **Ferrous (Fe²⁺)** complex of **protoporphyrin IX** arranged in **four pyrrole rings**. Each haem group is a **binding site for oxygen**.
- **Globin part:** **2α and 2β chains** are linked through **histidine** residues with one haem molecule.
- Hb exists in 2 forms: **T (taut)** form has low affinity for oxygen (**deoxyhemoglobin**); **R (relaxed)** form has high affinity for oxygen (**300X, oxyhemoglobin**).
- Hb exhibits **positive cooperativity and negative allostery** (accounts for **sigmoid** shaped oxygen dissociation curve for Hb), unlike myoglobin.
- **Positive cooperativity:** means that as oxygen binds to Hb, it facilitates binding of subsequent oxygen molecules, i.e. binding of the first oxygen molecule increases Hb's affinity for oxygen such that the fourth oxygen molecule binds to Hb at a much higher affinity than the first oxygen molecule.
- The **p50** of fetal Hb is less than that of adult Hb, i.e. p50 of HbF < HbA. (Note: p50 is the partial pressure of oxygen at which a protein is 50% saturated; lower values indicate greater affinity). Thus p50 of HbF is 19 mmHg whereas that of HbA is 26.8 mmHg.

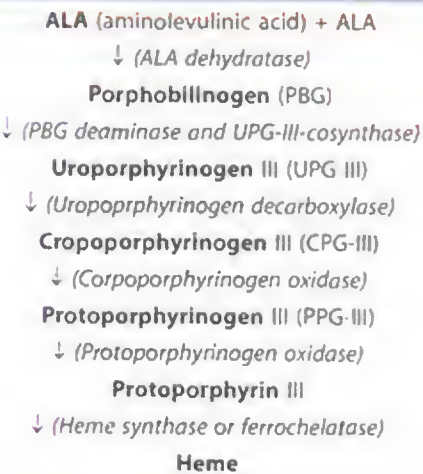
Normal Human Hemoglobins

Form	% of normal adult Hb	% of Hb at birth	Globin structure
HbA	97	25	α2β2
HbA ₂	2.4	Traces	α2δ2
HbF (foetal)	0.5	75	α2γ2

Hemoglobin Variants

Haemoglobin	Point mutation at	Aa substitution
HbS	β6	Glu → Val
HbC	β6	Glu → Lys
HbE	β26	Glu → Lys

Heme synthesis



Hemoglobin Modifications

1. Methemoglobin

- Form of **oxidised Hb** (Ferrous, Fe²⁺ replaced by **Ferric, Fe³⁺**), so that ability to carry oxygen is lost.
- **Methemoglobin** can avidly bind cyanide ion (CN⁻) and hence used in treating cyanide poisoning, where the iron in a fraction of the hemoglobin is deliberately oxidized by administration of **amyl nitrite**. The methemoglobin that is produced can sequester the circulating cyanide, thus preventing it from inhibiting electron transport.
- **Methemoglobinemia** can be treated with **methylene blue**.

2. Carboxyhemoglobin

- Haemoglobin combined with carbon monoxide (CO); **Affinity of Hb for CO is 200 times that for oxygen**, so CO will displace oxygen from Hb.
- Values > **60% carboxyhemoglobin** are fatal. CO poisoning is treated with oxygen therapy, which facilitates dissociation of CO.

Glycated hemoglobin (HbA1C)

- **Non-enzymatic binding** between adult HbA and glucose (α2β2-glucose).
- When once attached, glucose is not removed from the hemoglobin. Therefore it remains inside the erythrocyte, throughout the **lifespan (120 days)** of RBCs.
- Normal **HbA1C** levels are < 6%.
- Useful for providing a picture of **long-term diabetic control over past 2-3 months**.
- Albumin is also glycated in diabetes mellitus and **glycated albumin** reflects glucose control over **past 2-3 weeks** (since half life of albumin is 20 days).

Heme Catabolism

- Heme is scavenged from RBCs and Fe is reused. Heme → biliverdin → bilirubin (bilirubin is sparingly water soluble, toxic to CNS, transported by albumin).
- Heme is degraded primarily by a **microsomal** enzyme system **heme oxygenase**.
- Bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Some urobilinogen, an intestinal intermediate, is reabsorbed into blood and excreted as urobilin into urine.
- **Biliverdin** gives bruises their blue-green color.
- Jaundiced newborns are exposed to UV light, which converts bilirubin to urine-soluble products.
- **1 g of hemoglobin yields 35 mg of bilirubin**.

CSF

CSF Findings in Meningitis

	Bacterial (pyogenic) meningitis	TB meningitis	Viral meningitis
Opening pressure (mmHg, O)	200-500	180-300	< 250
Appearance	Often turbid	Opalescent (fibrin cob-web)	Usually clear
Cells	PMNs	Lymphocytes	Lymphocytes
Glucose	Low	Very low	Normal
Protein	High	Normal to high	Normal

EXTRA EDGE

- **CSF: Serum glucose ratio < 0.4** suggests **bacterial meningitis**.

Normal values

- **Volume** = 150 ml; Crystal clear fluid with pH = 7.3.
- **CSF pressure** = 50-180 mm CSF; 10-18 cm H₂O (lying on side); 30 cm H₂O (standing).
- Normal **opening pressure**: 7-18 mm CSF; in meningitis it may be > 40 (typically 14-30 mm CSF)
- **Lymphocytes** = < 4/mm³; Polymorphs = 0
- **CSF glucose** = 50-70 mg/dL; 2.8-4.4 mmol/L. (i.e. 2/3 of blood glucose level)
- **Protein** = 0.15-0.45 g/L
- **Chloride** = 20 mmol/L
- **Albumin: Globulin ratio** = 8:1
- 500-750 ml of CSF is produced per day.

- **Pathway of CSF flow** = Lateral ventricles (CSF secreted by cells of choroid plexus) → Interventricular foramina (of Monro) → 3rd ventricle → Cerebral aqueduct → 4th ventricle → Foramina in roof of fourth ventricle (Lateral foramina of Luschka and Median foramen of Magendie) → Subarachnoid space (CSF reabsorbed via the arachnoid villi into the dural venous system).

BILE ACIDS AND BILE SALTS

- Bile consists of a watery mixture of **organic and inorganic** compounds. **Phosphatidylcholine (lecithin)** and **bile salts** are quantitatively the most important organic component of bile.
- Bile can either pass directly from the **liver into the duodenum** through the common bile duct or be **stored in the gallbladder** when not needed immediately for digestion.

- The **rate-limiting enzyme** in bile acid synthesis is **7-α-hydroxylase**:
 - **Primary bile acids** = **cholic acid and chenodeoxycholic acid**. Bile acids are synthesized in the **liver from cholesterol**.
 - Before the bile acids leave the liver, they are conjugated to a molecule of either **glycine or taurine** – these new structures are called **bile salts** and include **glycocholic acid, taurocholic acid, glychenodeoxycholic acid** and **taurochenodeoxycholic acid**.
 - Intestinal bacteria can remove glycine and taurine from bile salts and convert them into **secondary bile acids** – **deoxycholic acid and lithocholic acid**.
 - **Bile salt deficiency** leads to **cholelithiasis** since the cholesterol is not kept in solution and this is called **lithogenic bile**.

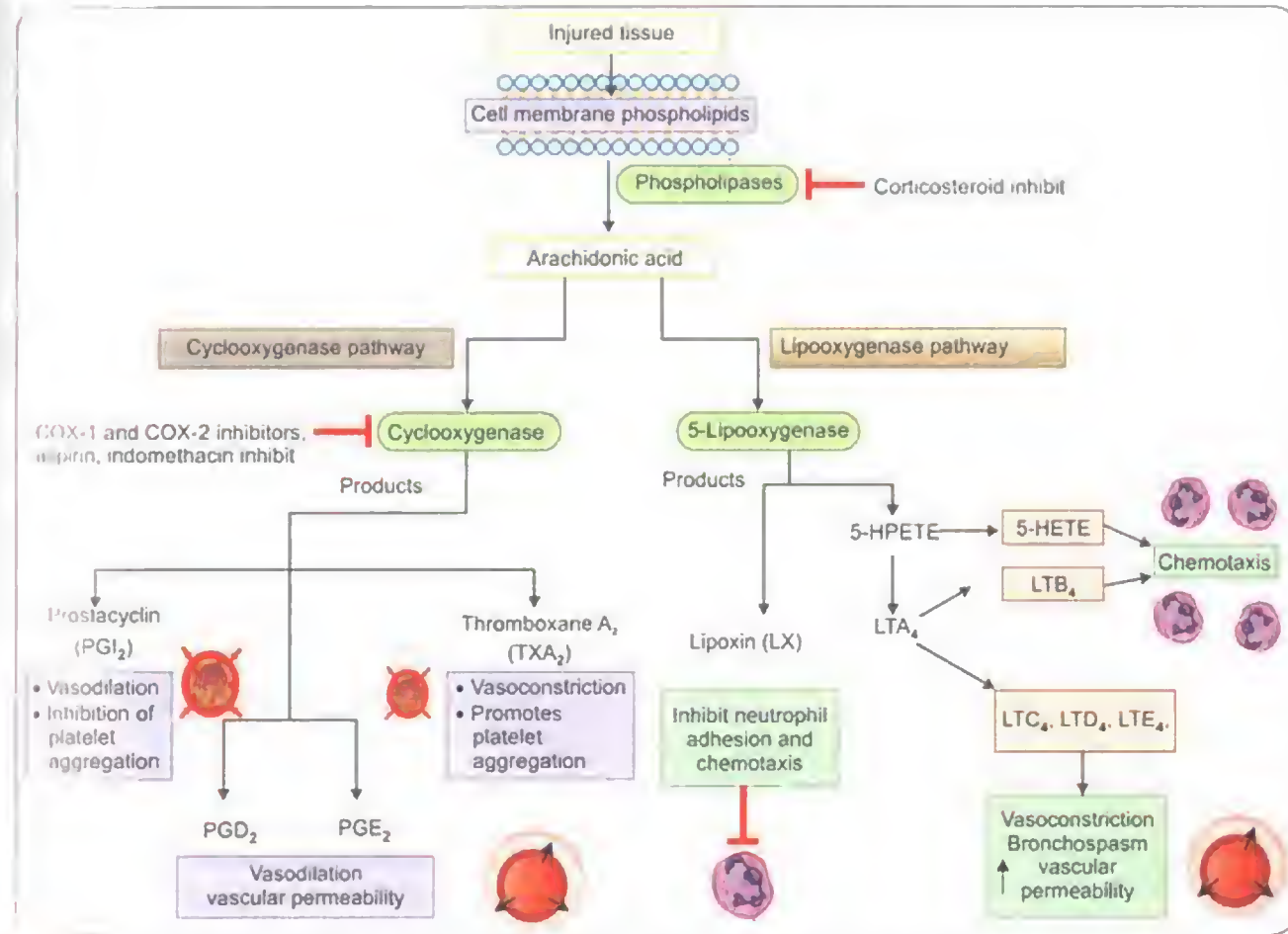


Fig. 13: Arachidonic acid metabolites involved in inflammation. The cyclooxygenase pathway generates prostaglandins (PGIs) and thromboxane (TXA₂). The lipoxygenase pathway forms lipoxins (LXs) and leukotrienes (LTEs). Abbreviation: COX, cyclooxygenase; HETE, hydroperoxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid

Enterohepatic Circulation of Bile Salts

- Of the total **bile salts** reaching the intestine, (15-30 g/day), only a very small fraction, **about 300-500 mg/day is excreted through feces**. The rest is **reabsorbed from the ileum, reaches the liver and re-excreted through the bile**. This is called **enterohepatic circulation**.
- When bile acid binding resin (**cholestyramine**) is given, the reabsorption of bile acids is inhibited. So only lesser quantity of bile acids are returned to the liver. Hence more cholesterol gets converted to bile acids and cholesterol is depleted.

Differential Diagnosis of Jaundice

	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Blood, free bilirubin	↑	↑	Normal
Blood, conj. bilirubin	Normal	↑	↑
Blood, alkaline phosphatase	Normal	↑	Very high
Urine, bile salts	Nil	Nil	Present
Urine, conj. bilirubin	Nil	Nil	Present
Urine, urobilinogens	↑	Nil	Nil

PORPHYRIAS

- Porphyrias** are a group of inherited or acquired disorders of certain enzymes in the heme biosynthetic pathway (also called porphyrin pathway). Based on the site of the overproduction and accumulation of the porphyrins (or their chemical precursors), porphyrias are broadly classified as:
 - **acute (hepatic) porphyrias**: characterized by **acute neurological attacks** (seizures, psychosis, extreme back and abdominal pain and an acute polyneuropathy).
 - **cutaneous (erythropoietic) porphyrias**: present with **skin problems**, usually a **sunlight-sensitive non-inflammatory blistering rash on dorsal surface of hands** and increased hair growth (**hypertrichosis**); low dose **hydroxychloroquine** useful in Treatment

➤ **Variegate porphyria (mixed porphyria)**, has both **neurological and skin features**.

- Porphyrias** = Disease of **5Ps** = **P**ain abdomen, **P**sychological disturbances, **P**olyneuropathy, **P**urple urine, **P**recipitated by **P**ills.

Classification of Human Porphyrias

Condition	Enzyme defect
Hepatic porphyrias	
Acute Intermittent porphyria (AD)	Porphobilinogen deaminase (uroporphyrinogen 1 synthase)
Porphyria cutanea tarda (AD), MC porphyria	Uroporphyrinogen decarboxylase
Hereditary coproporphyria (AD)	Coproporphyrinogen oxidase
Erythropoietic porphyrias	
Congenital erythropoietic porphyria (Gunther's disease) (AR)	Uroporphyrinogen cosynthase
Erythropoietic protoporphyria (AD)	Ferrochelatase (Heme synthase)
Mixed	
Variegate porphyria (AD)	Protoporphyrinogen oxidase

MORE HIGH YIELD TOPICS

Fasting and Starvation

- Priorities are to supply sufficient glucose to brain and RBCs and to preserve protein.

Days 1-3	<ul style="list-style-type: none"> Blood glucose level is maintained by Hepatic glycogenolysis and glucose release Adipose release of free fatty acids (FFA) Muscle and liver shifting fuel use from glucose to FFA Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA from odd chain FFA metabolism (the only triacylglycerol components that can contribute to gluconeogenesis) By 12-16 hours, glycogen stores are depleted.
After Day 3	<ul style="list-style-type: none"> Muscle protein loss is maintained by hepatic formation of ketone bodies, supplying the brain and heart
After several days	<ul style="list-style-type: none"> Ketone bodies become main source of energy for brain, so less muscle protein is degraded than during days 1-3.

EXTRA EDGE

- In starvation, the **activity of key gluconeogenic enzymes is increased**, viz. - Pyruvate carboxylase; Phosphoenolpyruvate carboxykinase; Fructose-1,6-bisphosphatase; Glucose-6-phosphatase (Pyruvate kinase activity **decreases** during starvation)
- In **fasting state RBCs** use only glucose.
- Rothera's test**: Nitroprusside in alkaline medium reacts with **ketone group** in urine to form a purple ring; this test is positive with acetone and acetoacetate BUT not with beta hydroxybutyrate.



Miscellaneous

- Isotopes**: elements, which have the same atomic number but different atomic weights, are called isotopes.
- Isoenzymes**: **Isoenzymes** are physically distinct forms of the same enzyme activity (eg.: **troponins**, **creatine kinase**)
- Avogadro number**: The number of molecules in one gram-molecular weight of any compound; defined as the number of atoms in 0.012 kg of pure carbon-12; it equals 6.02×10^{23}
- Synovial fluid** is highly viscous on account of the **hyaluronic acid**, which is present.
- The **ascorbic acid** content of **aqueous humor** is **20 times** that of plasma.

VITAMINS

Fat Soluble Vitamins

- Vitamin A, D, K, E**; ("All Doctors Know English!")
- Absorption **dependant on intestine (ileum) and pancreas**. Toxicity more common, than for water soluble vitamins, since these accumulate in the fat.

- They are **not excreted in urine** as they are hydrophobic; they may be toxic in excessive quantities.
- Malabsorption syndromes (steatorrhea)**, such as **celiac sprue, cystic fibrosis or mineral oil intake** can cause **fat soluble vitamin deficiencies**.

Water Soluble Vitamins

B₁ (Thiamine)
B₂ (Riboflavin)
B₃ (Niacin) "1-2-3...TALK!"
B₅ (pantothenic acid); "Panto = 5"
B₆ (pyridoxine); B-silX
B₁₂ (Cobalamin)
C (ascorbic acid)

EXTRA EDGE

- Water soluble vitamins **are excreted in urine** and hence cannot accumulate to toxic levels in the body.
- All B-complex wash out easily from the body except **B₁₂** and **folate** (stored in liver).
- Sulfur containing vitamins are Thiamine (B₁) and Biotin.
- Folic acid** and **Vit B₁₂** are called **hematopoietic vitamins** since they are required for normal maturation of RBCs because of their role in DNA synthesis.

Vitamin B₁ (Thiamine)

- Earlier called **aneurin**.
- Vit B₁ plays a central role in energy yielding **metabolism of carbohydrates**.

Sources	Cereals, grains, beans, pork
Deficiency	<ul style="list-style-type: none"> Seen in alcoholism, malnutrition Beri Beri (B₁ Deficiency = Ber₁ Ber₁) <ul style="list-style-type: none"> Dry Beriberi - polyneuritis, symmetrical muscle wasting Wet beriberi - high output cardiac failure (dilated cardiomyopathy), edema Wernicke's encephalopathy (ophthalmoplegia - Vl nerve MC, ataxia, confusion) ± Korsakoff's syndrome (retro and anterograde amnesia, confabulation, mamillary bodies affected). Lactic acidosis due to dysfunction of pyruvate dehydrogenase. B₁ deficiency can be assessed by checking RBC transketolase levels.
Function	<ul style="list-style-type: none"> Active form of thiamine is thiamine pyrophosphate (TPP), a.k.a. thiamine diphosphate (TDP). TPP is a cofactor for oxidative decarboxylation Pyruvate dehydrogenase in carbohydrate metabolism, which catalyses conversion of pyruvate to acetyl-CoA. Alpha-ketoglutarate dehydrogenase in TCA cycle, which catalyses conversion of alpha-ketoglutarate to succinyl CoA

Cond...

- Branched chain keto-acid dehydrogenase, which catalyzes oxidative decarboxylation of branched chain keto amino acids (leucine, isoleucine, valine).
- TPP is also a cofactor for *transketolase* in **HMP shunt**.

Vitamin B₂ (Riboflavin)

Sources	Milk
Deficiency	<ul style="list-style-type: none">• Angular stomatitis (oral mucosa inflammation),• Cheilosis, (lips inflammation)• Corneal vascularization;• "RiboFLAVin affects FLAVour (lips, mouth)!"
Function	<ul style="list-style-type: none">• Cofactor in oxidation and reduction• Enzymes containing riboflavin are called flavoproteins.• The two coenzymes are FMN (Flavin Mono Nucleotide) and FAD (Flavin Adenine Dinucleotide).<ul style="list-style-type: none">- FMN-dependent enzymes: L-Amino acid oxidase; NADH dehydrogenase- FAD dependent enzymes: Complex II of respiratory chain• Riboflavin is also called Warburg Yellow enzyme

Vitamin B₃ (Niacin)

Sources	Plants, meat, fish
Metabolism and excretion	<ul style="list-style-type: none">• Niacin can be formed in the body from tryptophan (<i>synthesis requires B₆</i>).• 1 mg of niacin is formed from 60 mg of tryptophan• Major metabolites of nicotinamide which are excreted in urine are N-methyl nicotinamide; N-methyl, 2-pyridone, 5-carboxamide (also called 2-pyridine) and 4-pyridine.• Nicotinic acid may be methylated to form trigonelline (N-methylnicotonic acid) or conjugated with glycine to form nicotinuric acid.
Function	<ul style="list-style-type: none">• Constituent of NAD⁺, NADP⁺ (used in oxidation-reduction - redox reactions).
Deficiency	<ul style="list-style-type: none">• Pellagra can be caused by Hartnup disease (↓ tryptophan absorption), malignant carcinoid syndrome (↑ tryptophan metabolism), and INH (↓ vitamin B₃)• Pellagra is also a/w diet rich in maize only or sorghum (jowar) only; both of these are poor in niacin and tryptophan and rich in leucine - BUT excess leucine inhibits conversion of tryptophan to niacin.• Pellagra: Deficiency of B₃ = 3Ds!: Diarrhea, photosensitive Dermatitis, Dementia;; also beefy glossitis occurs

Cond...

Cond...

- | | |
|-----------|--|
| | <ul style="list-style-type: none">• Casal collar/necklace: erythematous rash in a broad collar like distribution - C3/C4 dermatomes - seen in Pellagra. |
| Treatment | <ul style="list-style-type: none">• Niacin (nicotinamide) and diet rich in tryptophan• Niacin (B3) toxicity: fulminant hepatitis; glucose intolerance; hyperuricemia; macular edema and macular cysts. |

Vitamin B₅ (Pantothenic Acid)

Function	Constituent of Coenzyme A (CoA) and component of fatty acid synthase . Panthethine is the functional unit of these two coenzymes which is formed by combination of panothenate with cysteine . It provided thiol (-SH) prosthetic group of CoA and fatty acid synthase
Deficiency	Dermatitis, alopecia, enteritis, adrenal insufficiency

Vitamin B₆ (Pyridoxine)

Sources	Meat, fish, potatoes, bananas
Function	<ul style="list-style-type: none">• Pyridoxal phosphate (PLP) is the active form of vitamin B₆.• PLP is used as a cofactor used in<ul style="list-style-type: none">• Decarboxylation• Transamination• Condensation (delta-ALA synthase)• Transfluoration• Glycogen phosphorylase• Heme synthesis.• Synthesis of niacin from tryptophan• In B₆ deficiency, blood levels of homocysteine is increased - hence B₆ can be used in homocystinuria.
Deficiency	<ul style="list-style-type: none">• Peripheral neuropathy (BUT high doses can cause neurotoxicity)• Anemia• Convulsions• Hyper-Irritability• Oxalate kidney stones• Deterioration of Parkinsonism• PLP dependent conditions (where pyridoxine can be used in treatment are): homocystinuria; oxaluria; cystathionuria and xanthenuric aciduria.
Measurement of B ₆	<ul style="list-style-type: none">• RBC aspartate aminotransferase levels• Tryptophan load test: measuring urinary xanthenuric acid following a dose of tryptophan

Vitamin B₁₂ (Cobalamin)

Sources	<ul style="list-style-type: none">• Found ONLY in animal products - meat, egg, milk, fish• Stored primarily in liver. Very large reserve pool (lasts several years).• Small amount of B₁₂ is synthesized in intestine BY <i>Intestinal microorganisms</i>.• Absorption of vit B₁₂ from intestine (ileum) requires intrinsic factor (IF) of Castle secreted by parietal cells of stomach.• Vit B₁₂ is also called "extrinsic factor" of Castle.
Function	<ul style="list-style-type: none">• Cofactor for homocysteine methyltransferase.• Cofactor for methylmalonyl CoA isomerase: which catalyses conversion of methylmalonyl CoA into succinyl CoA; methylmalonic aciduria occurs in Vit B12 deficiency
Deficiency	<ul style="list-style-type: none">• Deficiency is caused by malabsorption (<i>enteritis, sprue, D.latum</i>), lack of intrinsic factor (<i>pernicious anemia, gastric bypass surgery</i>) or absence of terminal ileum (<i>Crohn's disease</i>).• Use Schilling's test to detect etiology of deficiency• Macrocytic, megaloblastic pernicious anemia• Neurological symptoms (subacute combined degeneration, <i>optic neuropathy, paresthesia</i>); glossitis• In vit B₁₂ deficiency, the conversion of N5 Methyl Tetra Hydro Folic Acid (THFA) to free THF is blocked. Most of the body folate is irreversibly trapped as N5 Methyl THFA - "THFA starvation with folate trap".• Imerslund-Gräsbeck syndrome = "Selective vitamin B12 (cobalamin) malabsorption with Proteinuria": AR disorder that appears in childhood . Characterized by vitamin B12 deficiency, megaloblastic anemia, failure to thrive and grow, Infections and neurological damage.

Folic Acid

Sources	<ul style="list-style-type: none">• Green leafy vegetables, dried beans and peas, lentils, liver. "FOLate from FOLiage".• Normal blood levels of folic acid = 2-20 nanogram/mL.
Function	<ul style="list-style-type: none">• Active form of folic acid is THF - tetrahydrofolate.• Major circulating form of folic acid is methyl THF.• Major point of entry for i-carbon transfer by substituted folate: methylene THF.• Coenzyme for (single) 1-carbon transfers; involved in methylation reactions.• Required for synthesis of bases in DNA and RNA.• Supplementary folic acid in early pregnancy reduces neural tube defects.• Recommended dose of folic acid in pregnancy is 400 micrograms/day (0.4 mg/day).
Deficiency	<ul style="list-style-type: none">• Macrocytic megaloblastic anemia due to defective DNA synthesis in RBCs.• FIGLU test: Histidine is normally metabolized to formimino glutamic acid (FIGLU) from which formimino group is removed by THF. Hence In folic acid deficiency, FIGLU is excreted in urine.• AICAR excretion: Amino imidazole carboxamide ribosyl-5 phosphate accumulates and is excreted in urine.

Biotin (Vitamin B₇ or Vitamin 'H')

Sources	<ul style="list-style-type: none">• Liver, egg yolk, cereals, yeast.
Deficiency	<ul style="list-style-type: none">• Caused by antibiotic use, excessive ingestion of egg whites (which contains avidin a protein that binds biotin and prevents its absorption).• Dermatitis, alopecia, paresthesia, enteritis
Function	<ul style="list-style-type: none">• Cofactor for carboxylations:• Pyruvate → oxaloacetate,• Acetyl CoA → Malonyl CoA• Propionyl CoA → Methylmalonyl CoA.

Vitamin C (Ascorbic Acid)

Sources	<ul style="list-style-type: none">Fresh fruits, <i>citrus fruits</i>, fresh vegetables.Maximum amount of vitamin C is found in <i>adrenal cortex</i>.
Deficiency	<ul style="list-style-type: none"><i>Scurvy</i> – <i>bruising, anemia, swollen gums, and poor wound healing</i>.
Function	<ul style="list-style-type: none"><i>Antioxidant</i> (free radical scavenger).Vit C is necessary for hydroxylation of proline and lysine in <i>collagen synthesis</i> - important in <i>wound healing</i>.Facilitates <i>iron absorption</i> by keeping iron in <i>Ferrous (Fe²⁺)</i> reduced state (more absorbable)Necessary as <i>cofactor for dopamine-β-hydroxylase</i> which converts <i>dopamine to norepinephrine</i>.Prophylactic against <i>neuroleptism</i><i>Vit C</i> is called “<i>respiratory catalyst</i>” - since it aids cellular respiration by acting as hydrogen transporter.

Vitamin A

Sources	<ul style="list-style-type: none">Liver, milk, butter, cheese, fish oils, orange and red colored fruits and vegetables (carrot, mango, papaya, pumpkin)
Basics	<ul style="list-style-type: none">Three major forms of vitamin A<i>Retinal</i> (an alcohol); <i>Retinol</i> (an aldehyde) and <i>retinoic acid</i> (an acid): All these mainly found in <i>animal foods</i>—milk, cheese, butter and oily fish.<i>Provitamin</i> of vitamin A - <i>Beta-carotene</i> is found in <i>green vegetables, red, and orange fruits</i> (carrots, tomatoes and apricots). Beta-carotene is converted in the body to <i>retinol in the small intestine</i>.
Function	<ul style="list-style-type: none"><i>Retinol</i> combines with light sensitive protein ‘opsin’ to form <i>rhodopsin (visual pigment)</i>.
Deficiency	<ul style="list-style-type: none"><i>Night blindness</i>, squamous metaplasia of corneal and conjunctival epithelium - <i>dry eyes</i> (<i>xerophthalmia</i> – <i>keratomalacia</i>) and Bitot’s spots, <i>dry skin</i> (<i>follicular hyperkeratosis</i>); pneumonia
Excess	<ul style="list-style-type: none"><i>Vitamin A toxicity</i>: Headache (<i>pseudotumor cerebri</i>); <i>arthralgia</i>; sore throat, liver damage, <i>bone damage</i>; alopecia; rupture of <i>lysosomal membrane</i>.

Vitamin D

- Vitamin D is also called “*hormonal vitamin*”.
- D2*= *ergocalciferol consumed in milk*
- D3* = *cholecalciferol, formed in keratinocytes in sun-exposed skin*
- 25-OH D3* = *storage form*
- 1,25 (OH)2D3 (calcitriol)* = *active form*

Sources	<ul style="list-style-type: none">Formed in sun-exposed skin
Function	<ul style="list-style-type: none"><i>Increases intestinal absorption of calcium and phosphate</i>
Deficiency	<ul style="list-style-type: none"><i>Rickets</i> in children; <i>osteomalacia</i> in adults. For further details on these conditions see <i>radioisotopes chapter (Pg 1164)</i>.
Excess	<ul style="list-style-type: none">Seen in <i>sarcoidosis</i> where the epithelioid macrophages convert vitamin D to its active form.<i>Hypercalcemia</i>, loss of appetite, stupor.

Sources	Green vegetables, dairy products
Deficiency	<ul style="list-style-type: none"><i>Neonatal hemorrhage</i> with PT and aPTT but normal bleeding time, because neonates have sterile intestines and are unable to synthesize vitamin K; <i>Neonates are given vitamin K injection at birth</i> to prevent hemorrhage.
Function	<ul style="list-style-type: none">Catalyzes <i>gamma-carboxylation</i> of residues on various proteins concerned with blood clotting.Newborns with inadequate vitamin K stores may develop <i>hemorrhagic disease of newborn</i>.Vitamin K dependent clotting factors are <i>2,7,9,10</i> and <i>protein C and S</i>.<i>Warfarin</i> and <i>dicaumarin</i> are vitamin K <i>antagonists</i>.

Vitamin E

- In animals vitamin E is called *anti-sterility vitamin*. It is present in *tocopherols*.

Sources	<ul style="list-style-type: none">Vegetable oils and seeds, almonds, nuts, spinach
Deficiency	<ul style="list-style-type: none">↑ fragility of Erythrocytes: hemolytic anemia (<i>E=Erythrocytes</i>)Neurodysfunction
Function	<ul style="list-style-type: none">Antioxidant actionPrevents rancidity of fatsHelps body to use vitamin K.

Vitamin K

- Forms of vitamin K are:
 - Vitamin *K₁* - *phyloquinone* (found in plants)
 - Vitamin *K₂* - *menaquinone* (synthesised by *intestinal bacteria*); So *vitamin K deficiency can occur after prolonged use of broad spectrum antibiotics*.
 - *Synthetic vitamin K₃* - *menadione*

TRACE ELEMENTS SUMMARY

Selenium	
Deficiency	Toxicity
<ul style="list-style-type: none"><i>Cardiomyopathy (Keshan disease)</i> endemic in children, young women in regions of China), Heart failure, Striated muscle degenerationSelenium (as <i>selenocysteine</i>) is a component of <i>glutathione peroxidase (antioxidant)</i> and <i>deiodinase</i> (thyroxine to tri-iodothyronine)	<ul style="list-style-type: none"><i>General</i>: Alopecia, nausea, vomiting, abnormal nails, emotional lability, peripheral neuropathy, lassitude, garlic odor to breath, dermatitis<i>Occupational</i>: Lung and nasal carcinomas, liver necrosis, pulmonary inflammation
Zinc	
Deficiency	Toxicity
<ul style="list-style-type: none"><i>Growth retardation</i>, loss of appetite, ↓ taste and smell, alopecia, <i>dermatitis and diarrhea (acrodermatitis enteropathica)</i>, <i>immune dysfunction</i>, failure to thrive, <i>gonadal atrophy</i>, congenital malformationsZinc is a cofactor for enzymes in DNA, RNA and protein synthesis. It is a constituent of <i>insulin, carboxypeptidase, carbonic anhydrase, LDH, alcohol dehydrogenase, alkaline phosphatase, superoxide dismutase</i>	<ul style="list-style-type: none">General: Reduced copper absorption, gastritis, sweating, fever, nausea, vomitingOccupational: Respiratory distress, <i>pulmonary fibrosis</i>
Calcium	
Deficiency	Toxicity
<ul style="list-style-type: none">Reduced bone mass, osteoporosis	<ul style="list-style-type: none">Renal insufficiency (<i>milk-alkali syndrome</i>), nephrolithiasis, impaired iron absorption
Iodine	
Deficiency	Toxicity
<ul style="list-style-type: none">Thyroid enlargement, ↓ T4, cretinism	<ul style="list-style-type: none">Thyroid dysfunction, <i>acne-like eruptions</i>
Copper	
Deficiency	Toxicity
<ul style="list-style-type: none"><i>Anemia (microcytic)</i>, growth retardation, defective keratinization and pigmentation of hair, hypothermia, degenerative changes in aortic elastin, osteopenia, mental deteriorationCopper is a constituent of <i>lysyl oxidase</i>; superoxide dismutase; cytochrome oxidase; ferroxidase; ceruloplasmin	<ul style="list-style-type: none">Nausea, vomiting, diarrhea, <i>hepatic failure</i>, tremor, mental deterioration, hemolytic anemia, renal dysfunction
Fluoride	
Deficiency	Toxicity
<ul style="list-style-type: none">Dental caries	<ul style="list-style-type: none">Dental and skeletal <i>fluorosis (renal tubular damage, parosteasias, interosseous membrane calcification, osteosclerosis)</i>
Iron	
Deficiency	Toxicity
<ul style="list-style-type: none">Muscle abnormalities, <i>koilonychia, pica, microcytic hypochromic anemia</i>, ↓ work performance, impaired cognitive development, premature labor, ↑ perinatal maternal mortality	<ul style="list-style-type: none">Gastrointestinal effects (nausea, vomiting, diarrhea, constipation), iron overload with organ damage, acute systemic toxicity
Manganese	
Deficiency	Toxicity
<ul style="list-style-type: none">Impaired growth and skeletal development, reproduction, lipid and carbohydrate metabolism; <i>upper body rash</i>	<ul style="list-style-type: none"><i>General</i>: Neurotoxicity, Parkinson-like symptoms<i>Occupational</i>: Encephalitis-like syndrome, <i>Parkinson-like syndrome</i>, psychosis, pneumoconiosis

EXTRA EDGE

- **Menkes disease: XLR**; connective tissue disease caused by **impaired copper absorption** and transport due to defective Menkes protein (**ATP7A**). Leads to decreased activity of **lysyl oxidase** (copper is a cofactor). Results in **brittle, 'kinky' hair**, growth retardation and hypotonia.
- **Loss of deep tendon reflexes** is an **early sign** of **hypermagnesemia**; other manifestations are **hypotension, bradycardia, lethargy and confusion**.

BIOTECHNOLOGY

DNA Analysis

- The DNA of a human chromosome contains about 108 base pairs, and before this DNA can be studied, fragmentation must occur. **Fragmentation** is used to break DNA into reproducible pieces of manageable size.
- Bacterial enzymes known as restriction endonucleases are used to cleave DNA at specific palindromic restriction sites of four to eight base pairs.
- Each restriction endonuclease cleaves a DNA molecule into a limited number of fragments of specific and reproducible sizes.
 - **Gel electrophoresis** is used to separate DNA fragments on the basis of size.
 - The **Sanger deoxynucleotide method** (chain termination) and the specific chemical cleavage procedure (Maxam-Gilbert) are two techniques used to determine the sequence of bases in DNA fragments.

Polymerase Chain Reaction (PCR)

- The PCR is **used to amplify very tiny (1-10 ng) pieces of DNA**.
- Steps:
 - **Denaturation**: DNA is denatured by heating to generate 2 separate strands
 - **Annealing**: during cooling, excess premade DNA primers anneal to a specific sequence on each strand to be amplified.
 - **Elongation**: heat stable DNA polymerase replicated the DNA sequence following each primer
 - These steps are repeated multiple times for DNA sequence amplification.
 - **Agarose gel electrophoresis**; used for **size separation of PCR products**.

DNA Fingerprinting

- This can be used to identify an **individual's DNA** and **to trace a family tree**. DNA from each individual has a characteristic DNA fingerprint.

- DNAs from different individuals contain sequence variations known as **polymorphisms**, which may involve an insertion or a deletion of one or more bases or a change in the sequence of bases.
- Some sequence polymorphisms occur in or near the sites of cutting by restriction enzymes. This leads to **restriction fragment length polymorphisms (RFLPs)**, which are differences in the sizes of restriction fragments between individuals.
- **Southern blotting** can be used to visualize RFLPs.

- **Southern blotting** = detects **DNA** fragments that contain a specific base sequence.
- **Northern blotting** = detects **RNA** fragments using hybridization probes.
- **Western blotting** = detects **Proteins**.
- **"SNOW DROP"**
- **South-Western blotting** = identifies **DNA binding proteins** (e.g., transcription factors) using oligonucleotide probes.

NUCLEIC ACIDS

Nucleotides

- **Pyrimidine** bases = cytosine, thymine, uracil.
- **Purine** bases = adenine, guanine.
- **Hypoxanthine** and **xanthine** are also **purines**, which occur as intermediates in metabolism of adenine and guanine.
- **Amino acids** necessary for **purine synthesis** = **glycine, aspartate** and **glutamate**.
- In humans **uric acid** is formed as the **end product of purine catabolism**.
- **Nucleoside** = composed of a purine or a pyrimidine base to which a sugar (usually either D-ribose or 2-deoxyribose) is attached in β -linkage at N9 or N1 respectively.
- **Nucleotides** = phosphorylated nucleosides (phosphate group attached by ester linkage to C5).
- Various **ribonucleotides** are adenosine, guanosine, cytidine, uridine.
- Various **deoxyribonucleotides** are deoxyadenosine, deoxyguanosine, deoxycytidine and thymidine.
- **Pseudouridine**: In uridine, ribose is attached to N1 of uracil by a C-N bond. But in pseudouridine, which occurs particularly in **t-RNA**, ribose is attached to C-5 of uracil by a C-C bond.
- **Adenosine derivatives** = adenosine tri-phosphate (ATP), ADP and S-AdenosylMethionine (SAM, a form of active methionine).

- Organisms that excrete nitrogen waste product as uric acid (birds, amphibians, reptiles) are **uricotelic**, whereas those which excrete urea (humans) are **ureotelic**.
- The most important regulator of de novo purine biosynthesis is the intracellular concentration of **PRPP (phosphoribosyl pyrophosphate)**.
- **Gout**: **sodium urate** crystals, **needle shaped, negatively birefringent** in polymorphs of synovial fluid.
- **Pseudogout** = **Calcium pyrophosphate** crystals, **positively birefringent** in synovial fluid are; **Knee MC** affected joint.

Disorders Caused by Deficiencies in the Enzymes Involved in Nucleotide Metabolism

Lesch-Nyhan syndrome	Hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency - Cell breakdown products cannot be reused . Excessive purine synthesis, hyperuricemia , spasticity, mental retardation, self-mutilation , gout , choreoathetosis . Allapurinol decreases deposition of sodium urate crystals, but does not ameliorate the neurologic symptoms.
Severe combined immunodeficiency (SCID)	Adenosine deaminase (ADA) deficiency; T-cell and B-cell dysfunction with early death from overwhelming infection. SCID is first human disease successfully treated by gene therapy ; ("SCID affects Kids!!")
Hereditary orotic aciduria	Orotate phosphoribosyl transferase and/or OMP decarboxylase deficiency; Retarded growth and severe anemia. Feeding of synthetic cytidine or uridine supplies the pyrimidine nucleotides needed for RNA and DNA synthesis, restores normal growth, and reverses the anemia.

Nucleic Acids

- DNA contains Adenine, **Thymine**, Guanine, Cytosine (**ATGC**) and deoxyribose sugar.
- RNA contains Adenine, **Uracil**, Guanine, Cytosine (**AUGC**) and ribose sugar.

DNA Structure

- **Watson, Crick** and **Wilkins** proposed the **double helix** model of DNA in early 1950s.
- There are 6 forms of DNA, A to E and Z. **B form** is **MC**.

- In DNA, concentrations of **A = T** and **G = C**. These are held together (A with T and G with C) by **hydrogen bonds** (two between A and T; and three between G and C).
- The two strands of the double helix are **right handed** (except **Z DNA** which is **left handed**) and are **anti-parallel**.
- Each turn of the helix has a length of **34 Angstroms** (known as the **pitch** of the helix).
- **Chargaff's rule** state that DNA from any cell of all organisms should have a 1:1 ratio (base Pair Rule) of pyrimidine and purine bases and, more specifically, that the amount of **guanine** = **cytosine** and the amount of **adenine** = **thymine**.
- **Example of Chargaff rule**: If the sample of DNA in adenine is 23%, what will be the amount of guanine present? (PGI May 2013) - Based on Chargaff rule. A = T; so A + T = 46%; Rest 54% is G + C; since G = C, the amount of Guanine is 54/2 = 27%.

Non-Watson Crick Base Pairs

Here, base pairing does not occur according to the Watson Crick base pairing rule. These include:

- **Wobble base pairs**: Occurs due to **tautomerism**; G-T and A-C are more common; occur more commonly in **tRNAs**; play an important role in **codon-anticodon interactions**.
- **Haagsteen base pairs**: Form the basic structural units in **triple-helix DNA (triplex or H-DNA)**.
- **Reverse Watson-Crick base pairs**: Form the basic structural unit in **parallel-stranded DNA (psDNA)**.

Properties of DNA

- **Denaturation** (melting) of DNA: The double stranded structure of DNA can be melted in solution by increasing the temperature or decreasing the salt concentration.
- **Hyperchromicity** of denaturation: Concomitant with this denaturation of the DNA molecule is an increase in the optical absorbance of the purine and pyrimidine bases—a phenomenon referred to as **hyperchromicity of denaturation**.
- **Annealing**: If the heat denatured DNA is slowly cooled, the denaturation is reversible, the helical structure is reformed and the two strands get together. This is "annealing".
- **Quenching**: Rapid cooling of the denatured DNA fixes it in a permanently denatured state and is called "quenching".

DNA Replication

- Replication is **semi-conservative**, i.e. each daughter molecule receives only one strand from the parent DNA molecule.
- Discontinuous replication**, i.e. one or both strands may be synthesised in pieces called **Okazaki fragments** (fragments of DNA attached to an RNA initiator component, which are then linked together to yield a continuous DNA chain).

- **DNA ligases** are essential for the joining of **Okazaki fragments** during replication, and for completing short-patch DNA synthesis occurring in DNA repair process.
- **Helicase**: unwinds DNA template at replication fork.
- **DNA topoisomerases**: create a nick in the helix to relieve supercoils created during replication
- **DNA polymerase** synthesises the new strand in 5' to 3' direction.
- **Primase**: makes an RNA primer on which DNA polymerase can initiate replication.
- **Telomerase**: It **adds DNA (TTAGGG)** to 3' end of chromosomes; has **reverse transcriptase (hTERT) function**; **stem cells and cancer cells express high levels of telomerase** that prevent telomere shortening to critical levels and allow **indefinite cell proliferation**:
 - **Cre (Couse recombination) recombinase** is a 38 kDa enzyme isolated from the P1 bacteriophage. It efficiently binds to **loxP sites**.

EXTRA EDGE

- There are 5 types of mammalian (eukaryotic) DNA polymerases (DNAP):
 - Alpha DNAP – majorly responsible for **chromosome replication**; **primase activity** is present.
 - Beta DNAP is a **repair** enzyme.
 - Gamma DNAP is concerned with **mitochondrial DNA** synthesis.
 - Delta DNAP is used for **both leading and lagging strand** synthesis.
 - Epsilon DNAP is used for **leading strand** synthesis.
- Magnesium (Mg²⁺)** has a stabilizing effect on DNA and chromatin structure, and is an essential cofactor in almost all enzymatic systems involved in **DNA processing and replication**.

Genetic Code Features

- Unambiguous**: Each codon specifies only 1 amino acid
- Degenerate/redundant**: More than 1 codon may code for the same amino acid (exception IS: methionine and tryptophan encoded by only 1 codon, AUG and UGG respectively)

- Commaless, nonoverlapping**: Read from a fixed starting point as a continuous sequence of bases
- Universal**: Genetic code is conserved throughout evolution.

Mutations in DNA

- Silent**: Same amino acid, often base change in 3rd position of codon (tRNA wobble).
- Misense**: Changed amino acid (conservative – new amino acid is similar in chemical structure).
- Nonsense**: Change resulting in early STOP codon.
- Frame shift**: Change resulting in misreading of all nucleotides downstream, usually resulting in a truncated nonfunctional protein.

RNA

- Single** stranded; 90% is present in the **cytoplasm** and 10% in the nucleolus. Guanine content does not necessarily equal its cytosine content, nor does its adenine content equal its uracil content.

Messenger RNA (mRNA) Is the **template** for polypeptide synthesis, **longest RNA**; (**mRNA** = **Mega**RNA)

Transfer RNA (tRNA) brings activated amino acids into position along the mRNA template. It forms a **cloverleaf structure** that contains many unusual nucleotides, **smallest RNA**; (**tRNA** = **tiny** RNA)

tRNA "Wobble": Accurate base pairing is required only in the first 2 nucleotide positions of an mRNA codon, so codons differing in the 3rd "wobble" position may code for the same tRNA/amino acid.

Ribosomal RNA (rRNA) is a component of ribosomes, which functions as a **non-specific site of polypeptide synthesis**; **most abundant RNA** (80%) in cell; (**rRNA** = **rampant** RNA)

Transcription

- Takes place in **nucleus**.
- Synthesis of complete **RNA molecules from DNA** One of the two DNA strands acts as a template for the creation of an mRNA molecule with a complementary base sequence.
- Transcription yields three types of RNA**: mRNA, tRNA and rRNA.
- Fully conservative replication. Synthesis in 5' → 3' direction.

- DNA-dependent RNA polymerase** is required (see Note).
- Processing**: the RNA must be further modified to make it functionally active, e.g. introns cut out, exons spliced and in some cases polyadenylation before delivery of mRNA to the cytoplasm.
- Note**: Unlike DNA polymerase, RNA polymerase can initiate the synthesis of new strands. The RNA of an RNA virus is replicated by an RNA-dependent RNA polymerase. Oncogenic RNA viruses synthesize DNA from RNA, and insert the DNA into the chromosomes of animal cells. This reverse transcription is mediated by an RNA-directed DNA polymerase (**reverse transcriptase**).
- Note**: Nuclear pre-mRNA splicing is catalysed by the **spliceosome**, a multi megadalton ribonucleoprotein (RNP); two major types are U2 and U12 dependant.

Translation

- Takes place in **cytoplasm**.
- Protein synthesis according to the amino acid code in mRNA.
- Occurs on ribosomes when a tRNA molecule with three bases (anticodons) specific for a particular amino acid binds to the complementary mRNA codon.
- 3 stages:
 - **Amino acid activation**
 - **Initiation**: of polypeptide chain formation begins with the amino acid, methionine (methionine coded by AUG codon which **inAUGurates** protein synthesis).
 - **Elongation**: of chain in 5' → 3' direction.

- **Termination**: of the chain by one of three terminator codons, UGA, UAA and UAG. (**UGA** = **U** Go Away; **UAA** = **U** Are Away; **UAG** = **U** Are Gone!!).

EXTRA EDGE

- Mnemonic: TransCription: Nucleus; TransLation: cytoPlasm ("Chor Never Likes Police!")

Other RNAs

snRNA (small nuclear RNA) Plays **structural and catalytic roles** in **spliceosomes**, the complex of protein and RNA that splice pre-mRNA; The **U7 snRNA** (U7 snRNP) is an RNA molecule involved in the 3' end formation of **histone pre mRNAs**.

snoRNA (small nucleolar RNA) Aids in **processing of pre-rRNA transcripts** for ribosomal subunit formation in the nucleolus

siRNA (small Interfering RNA) and miRNA (microRNA) Are involved in **regulation of gene expression**

SRP RNA Is a component of the **signal recognition particle (SRP)**, the protein RNA complex that recognizes the signal peptides of polypeptides targeted to the ER

EXTRA EDGE

- RNA interference (RNAi)** is a means of silencing genes by way of **mRNA degradation**. **Gene knockdown** by this method is achieved by introducing small double-stranded interfering RNAs (siRNA) into the cytoplasm.

Microbiology

HISTORY

Important People

Scientist	Contribution
Hieronymus frascatorius	Theory of Contagion
Louis Pasteur	Father of Microbiology
Robert Koch	Father of Bacteriology
Paul Ehrlich	Father of Chemotherapy
Joseph Lister	Father of Modern Antiseptic Surgery
Edward Jenner	Father of Immunology
Antonie Van Leeuwenhoek	Invented simple microscope ; a Dutch (Holland/Netherlands) lens grinder
McMahon and Pugh	Theory of web of causation
Ernst Ruska	Inventor of electron microscope
Alexander Fleming	Discovered penicillin
Metchnikoff	Described phagocytosis and coined the term phagocyte
Sanger and Gilbert	Were the first to develop method of DNA sequencing
Kary B Mullis	Invented PCR (polymerase chain reaction) and won the Nobel prize in 1993



Fig. 5.1: Antonie Van Leeuwenhoek

Contributions of Louis Pasteur

- Coined the term '**microbiology**'
- Coined the term '**vaccine**'
- Proposed **germ theory** of disease
- Disapproved theory of spontaneous generation (**abiogenesis**)
- Developed sterilization techniques
- Studies on pebrine (silkworm disease); anthrax, chicken cholera and hydrophobia
- Developed live attenuated **anthrax vaccine**
- Developed **rabies vaccine**.



Fig. 5.2: Louis Pasteur

Contributions of Robert Koch

- Developed **Hanging drop** method.
- Isolated pure cultures of bacteria.
- Koch's phenomenon of hypersensitivity.
- Discovered *M tuberculosis*, *B anthracis* and *V cholerae*.
- **Koch's postulates**:
 - Organism should be regularly found in the lesions of the disease.
 - It should be possible to isolate the organism in pure culture from the lesions.
 - Inoculation of pure culture into the suitable lab animals should reproduce the lesions of the disease.

- It should be possible to reisolate the organism in pure culture from the lesions produced in experimental animals.
- NEW postulate later added-specific antibodies should be demonstrable in the serum on patients suffering from the disease.
- Organisms that DO NOT meet the criteria of Koch's postulates are:
 - *Mycobacterium leprae* and *Treponema pallidum* (cannot be cultured *in vitro*).
 - *Neisseria gonorrhoeae* (there is no animal model).
- Molecular Koch postulate—by Stanley Falkow, stated that gene (coding for virulence) of a microorganism should satisfy all the criteria of Koch postulates rather than the microorganism itself.



Fig. 5.3: Robert Koch

More Historical One-Liners

- **Edward Jenner** discovered the **smallpox vaccine** in 1796—the **first vaccine** to be discovered.
- Antonie Van **Leeuwenhoek** described the bacteria seen under microscope as '**little animalcules**'.
- Theory of **spontaneous generation (abiogenesis)** was put forth by English priest—**John Needham**.
- **Salvarsan (magic bullet)**—an **arsenical** compound to cure **syphilis** was introduced by **Paul Ehrlich**.
- The first human disease proved to be of viral origin was yellow fever by **Walter Reed**.
- **Schaudin** and **Hoffman** discovered *Treponema Pallidum* in 1905.
- **Ronald Ross** discovered that **malaria is transmitted** by female anopheles mosquito.
- **Selman Waksman** developed streptomycin and coined the term '**antibiotic**'.

BACTERIOLOGY

Bacteria and their Alternate Names

<i>Bordetella</i>	Bordet gengou bacillus
<i>Clostridium tetani</i>	Nicalaire's bacillus
<i>Corynebacterium diphtheriae</i>	Klebs-Löffler bacillus
<i>Carynebacterium pseudotuberculosis</i>	Preisz Nacard bacillus
<i>Corynebacterium pseudodiphtheriticum</i>	Hoffman's bacillus
<i>Eberth Gaffky bacillus</i>	Salmonella
<i>Hoemophilus oegyptius</i>	Koch weeks bacillus
<i>Hemophilus influenzae</i>	Pfeiffer's bacillus
<i>Klebsiella pneumoniae</i>	Friedlander's bacillus
<i>Klebsiella ozaenae</i>	Abel's bacillus
<i>Klebsiella rhinoscleromatis</i>	Frisch bacillus
<i>Mycobacterium tuberculosis</i>	Koch's bacillus
<i>Mycobacterium Intracellulare</i>	Bathey bacillus
<i>Mycobacterium paratuberculosis</i>	Johne's bacillus
<i>Mycobacterium leproe</i>	Hansen's bacillus
<i>Mycoplasma</i>	Eoton agent
<i>Pseudomonas pseudomallei</i>	Whitmore's bacillus
<i>Salmonella typhi</i>	Goffly Eberth bacillus
<i>Staphylococcus aureus</i>	Ogston's microbe

Meanings of some terms

- **Anthrox** = Coal
- **Chlamys** = Mantle or toga
- **Clastridia** = Spindle
- **Caryne** = Club
- **Diphtheras** = Leather
- **Ganorrhoea** = Flow of seed
- **Hemophilus** = Blood loving
- **Leptos** = Fine, thin
- **Proteus** = Pleomorphism
- **Stophyle** = Bunch of grape
- **Streptas** = Twisted or coiled

EXTRA EDGE

- All cocci are gram-positive **except** *Neisseria*.
- All bacilli are gram-negative **except** **DATTA**: *Diphtheria*, *Actinomyces*, *Tetani*, *Tuberculosis mycobacterium*, *Anthrax bacillus*.

Motility of Organisms

Motility	Organism
Falling leaf motility	Giardia intestinalis (lamblia) trophozoites
Darting motility or swarm of gnats	Cholera organisms, Campylobacter, Gardnerella
Stately motility	Clostridia
Swarming motility	Proteus, B cereus, Cl tetani
Spinning motility	Fusobacterium gyrans
Tumbling motility	Listeria
Gliding motility	Mycoplasma
Corkscrew motility	T pallidum
Lashing motility	Borrelia

Shapes of Bacteria

Gram positive cocci arranged in	
Cluster	Staphylococcus
Chains	Streptococcus
Pairs (lanceolate)	Pneumococcus
Tetrads	Micrococcus
Octate	Sarcinia
Pairs (spectacle eye shaped)	Enterococcus

Gram positive bacilli arranged in	
Chain (bamboostick)	Bacillus anthracis
Chain	Streptobacillus
Palisades, V or L shaped or cuneiform	Corynebacterium

Gram negative cocci arranged in	
Pairs (lens shaped)	Meningococcus
Pairs (kidney shaped)	Gonococcus

Gram negative bacilli arranged in	
Spirally coiled rigid	Spirillum
Spirally coiled flexible	Spirochete
Comma shaped	Vibrio cholerae
Curved	Campylobacter (Gull wing shaped) and Helicobacter

Urease positive organisms

- > Proteus
 - > Ureaplasma
 - > Nocardia
 - > Cryptococcus
 - > H pylori
 - > Brucella
 - > Yersinia enterocolitica
- PUNCH BY**

Colony Appearances

Colony appearance in culture	Organism
Bamboostick; medusa head; inverted fir tree appearance	Bacillus anthracis
Thumb print appearance, bisected pearls or mercury drops, aluminium paint appearance	Bordetella pertussis
School of Red fish	Hemophilus ducreyi
Sotellitism	Hemophilus Influenzae
Nogler's reaction	Clostridium perfringens
Fried egg colony	Mycoplasma
Lenticular shaped	Neisseria meningitidis
Draughtsman (concentric rings) appearance	Pneumococcus
Swarming growth (fishy, seminal smell)	Proteus
Oil paint appearance	Staphylococcus
Stalactite growth in ghee brath	Yersinia pestis
Daisy head colony	C diphtheriae (gravis)
Frog's egg colony	C diphtheriae (intermedius)
Poached egg colony	C diphtheriae (mitis)

Selective Media

Organism	Medium
Bacillus anthracis	PLET medium
Bacillus cereus	MYPA (Mannitol Egg Yolk)
Bordetella	Bordet gengou medium; Regan Lou medium, Lacey's DFP medium
Brucella	Castaneda method of blood culture
Burkholderia	Ashdown's medium
Campylobacter jejuni	Campy Bap, Skirrow's or Butzler's media
Chlamydiae	Tissue culture (irradiated McCoy cells, HeLa cells treated with DEAE dextran)
Clostridia (anaerobic organisms)	Robertson's cooked meat broth, Thioglycollate, Smith Noguchi
Corynebacterium diphtheriae	Loeffler's serum slope
Legionella	BCYE (Buffered charcoal yeast extract)
Listeria	PALCAM agar
Leptospira	EMJH medium; Fletcher medium; Korthof medium; Stuart's medium

Contd...

Contd

Organism	Medium
Mycobacterium tuberculosis	Lowenstein Jensen (LJ) medium; Middle Brook's medium, Dorset Egg medium
Mycoplasma	PPLO medium
Neisseria gonorrhoeae	Thayer Martin medium Chacko nair medium
Pseudomonas	Cetrimide agar
Neisseria	Yolk sac of developing chick embryo
Shigella	Deoxycholate Citrate agar (DCA)
Spirochaetes	Noguchi's medium
Staphylococcus	Ludlam's medium
Trypanosomes	Novy, MacNeal, Nicole medium
To differentiate lactose and non-lactose fermenters	MacConkey's medium

Transport Media

Streptococcus Pyogenes	Pike's medium
V cholerae	Cary Blair medium, Venkatraman Ramakrishnan (VR) medium, Autoclaved sea water
Neisseria	Stuart's medium, Amie's medium
Salmonella, Shigella	Sach's Buffered glycerol saline
Bordetella	Modified Stuart's; Mischulow's charcoal agar

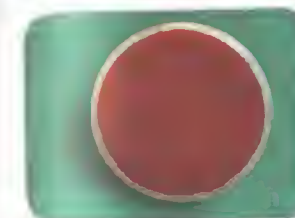


Fig. 5.4: Blood agar



Fig. 5.5: Chocolate agar



Fig. 5.6: Loeffler's serum slope (LSS)



Figs 5.7A and B: LJ media without growth and with growth

Pigment-Producing Bacteria

Pseudomonas	Green
Staph aureus	Golden yellow
Rhodococcus	Red
Bacteroides melanogenicus	Black
Nocardia	Yellow to Red

Spore-Forming Bacteria

- Bacillus anthracis and subtilis
 - Sporosarcina
 - Clostridia
 - Coxiella
- 'BSC Chemistry!'

Zoonotic Bacteria

Species	Disease
Bartonella HENSelae	Cat scratch fever - In lymphadenopathy; Bacillary angiomatosis causes diffuse skin hemangiomas typically seen in AIDS patients; also peltasis hepatitis Transmitted by Cat scratch (Cat Scratched the HEN!)
Bartonella quintana	Trench fever with abrupt onset fever; Seen in crowded unsanitary conditions
Brucella spp	Undulant (Molto) fever = fever waxes and wanes over months, hepatosplenomegaly; transmitted by UNpasteurized dairy products; contact with sheep/cattle
Francisella tularensis	Tularemia, ulceroglandular, i.e. ulcer with adenopathy; Transmitted by Tick bite; rabbits, deer
Yersinia pestis	Plague, buboes and rapid sepsis; Transmitted by Flea bite; rodents
Posteurella multocida	Cellulitis; From dog or cat bites
Capnocytophaga	Endogenous to mouth of dogs; transmitted by dog bites

Diseases Transmitted Through Raw Cow's Milk

- Listeriosis
 - Anthrax
 - Brucellosis
 - Salmonellosis
 - Campylobacteriosis
 - Q fever
 - EHEC
 - Staph/Strep. mastitis
 - Tuberculosis
- 'LABS CQuEST'

MORPHOLOGY AND PHYSIOLOGY OF BACTERIA

- **Prokaryotes** are evolutionally ancient and are not capable of carrying off life processes by themselves since they lack the organelle. Examples are *bacteria* (including chlamydia and mycoplasma), *blue-green algae* and *archaea* (archebacteria).
- **Eukaryotes** (meaning 'true nucleus') contain all cell organelle required to carry out the processes of life. Examples are *fungi*, *protozoa* and *algae* (other than blue green algae).

	Prokaryotes	Eukaryotes
Nucleus	Absent	Present
Nuclear membrane	Absent	Present
Nucleolus	Absent	Present
Deoxyribonucleoprotein	Absent	Present
Chromosome	One (circular)	More than one (linear)
Mitotic division	Absent	Present
Cytoplasmic streaming	Absent	Present
Pinocytosis	Absent	Present
Mitochondria	Absent	Present
Lysosomes	Absent	Present
Golgi apparatus	Absent	Present
Endoplasmic reticulum	Absent	Present
Sterols	Absent	Present
Muramic acid	Present	Absent

Bacterial Cell Walls

Common to Both Gram Positive and Gram Negative

- **Flagellum** (motility)
- **Pilus** (for bacterial adherence to cell surface; sex pilus during conjugation)
- **Capsule** (protects against phagocytosis; polysaccharide except *B anthracis* which contains *D-glutamate*)
- **Peptidoglycan**—composed of N-acetyl glucosamine and N-acetyl muramic acid (gives rigid support, protects against osmotic pressure)
- **Cytoplasmic membrane**.

Unique to gram positive organisms	Unique to gram negative organisms
-----------------------------------	-----------------------------------

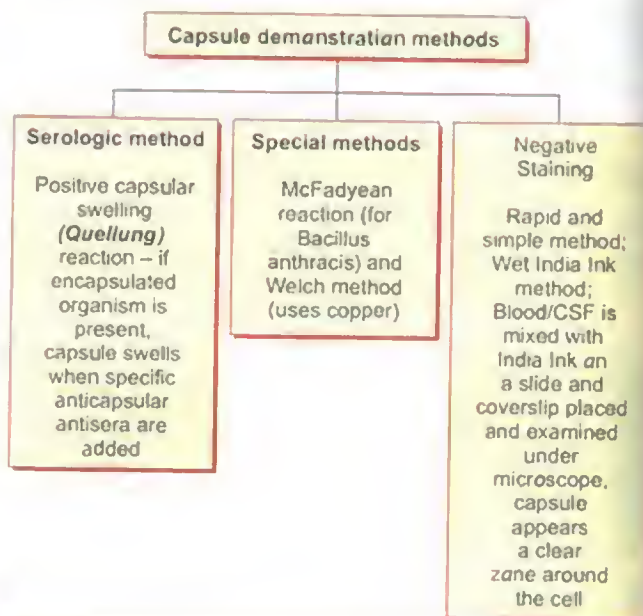
- | | |
|---|---|
| <ul style="list-style-type: none"> • Cell wall is thicker, fewer amino acids • Contains Teichoic acid which induces TNF and IL-1 | <ul style="list-style-type: none"> • Cell wall is thinner contains more amino acids including aromatic and sulfur containing amino acids • Endotoxin/lipopolysaccharide (outer membrane); major surface antigen • Periplasmic space (space between cytoplasmic membrane and outer membrane; contain many hydrolytic enzymes including β-lactamases) |
|---|---|

EXTRA EDGE

- **Mycoplasma**: contain **sterols** and have NO cell wall; they represent **L-forms** of bacteria.
- **Mycobacteria**: cell wall contains **mycolic acid**; **high lipid** content.
- **Cytoplasmic membrane** acts as a **semipermeable** membrane (selectively permeable) controlling the flow of metabolites to and from the cytoplasm.
- **Mesosomes (chondroids)** are formed by invagination of plasma membrane into the cytoplasm—they are more prominent in gram positive bacteria; they are the main site of **respiratory enzymes** in bacteria (analogous to mitochondria of eukaryotes).

Bacterial Capsule

- Bacterial capsule is usually composed **polysaccharide**, except in *Bacillus anthracis*—it is made up of **polypeptide** (protein, *D-glutamic acid*).
- The polysaccharide capsule is an antiphagocytic virulence factor. **Capsule serves as antigen in vaccines** (Pneumovax, Hib, Meningococcal vaccines).



Encapsulated bacteria

- *Str. Pneumoniae*
 - *Klebsiella pneumoniae*
 - *Hemophilus influenzae B*
 - *Pseudomonas aeruginosa*
 - *N. meningitidis*
 - *Cryptococcus*
- 'Same Killers Have Pretty Nice Capsules!'

Metachromatic Granules

- Also **polymetaphosphate** granules, **volutin** granules, **Rubens Ernst** granules or **polar** bodies.
- These granules stain **reddish violet with methylene blue** or **toluidine blue**—strongly **basophilic**.
- These granules are seen in: *Corynebacterium diphtheriae*, *Gardnerella vaginalis* and *Spirillum volutans* (first described in this bacteria—hence called volutin granules!).
- Metachromatic granules are stained with special stains: **Loeffler's methylene blue**, **Albert's**, **Neisser's**, **Ponder's** stains.

Flagella

- Flagella are organs of locomotion; all motile bacteria except for spirochetes possess flagella.
- Flagella are made up of protein antigen flagellin.
- Flagella may be:
 - **Monotrichous**: Single polar flagellum (at one end, e.g. *V. cholerae*).
 - **Amphitrichous**: Single flagellum at both ends, e.g. *Alkaligenes fecalis*.
 - **Lophotrichous**: Tuft of flagella at one or both ends, e.g. *Spirilla*.
 - **Peritrichous**: Flagella surrounding the cell, e.g. *typhoid bacilli*.

Fimbria (Pili)

- **Ordinary (common) pili**: Functions as organs of adhesion
- **Sex pili**: Appear to be involved in transfer of DNA during conjugation.

Bacterial Toxins

Endotoxins	Exotoxins
Lipopolysaccharide in nature	Proteins (polypeptides)
Heat stable	Heat labile (> 60°C)
Form integral part of cell wall, released only on disruption of bacterial cell	Actively secreted by living cells into the medium
Weakly antigenic ; antitoxin is not formed but antibodies against polysaccharide are raised	Highly antigenic; stimulates formation of antitoxin, which neutralizes toxin
Cannot be toxoided	Converted into toxoid by formaldehyde

Contd...

Endotoxins	Exotoxins
Not enzymic action	Enzymic in action
Non-specific action of all endotoxins	Specific pharmacological effect of each exotoxin
Low potency	Very high potency
Non-specific in action	Highly specific for particular tissue, e.g. tetanus toxin for CNS
Usually produce fever	Do not produce fever in host
Produced by Gram-negative bacteria	Produced mainly by Gram-positive bacteria and also by some Gram-negative bacteria

Exotoxins and their Mechanism of Action

Exotoxin	Mechanism
<i>Enterotoxin</i> and <i>TSST</i> of <i>S aureus</i>	Act as superantigen ; stimulate T-cell non-specifically, to release large amounts of cytokines
<i>Streptococcal</i> pyrogenic exotoxin	
<i>Diphtheria</i> toxin and exotoxin A of <i>Pseudomonas</i>	Inhibits protein synthesis (by inhibiting EF-2)
<i>Anthrax</i> toxin	↑ cAMP in target cells, edema
<i>Alpha</i> toxin of <i>Clostridium perfringens</i>	Lecithinase and phospholipase activity—causes myonecrosis
<i>Tetanus</i> toxin (<i>tetanus spasm</i>)	Decrease in neurotransmitter (GABA and glycine) release from inhibitory neurons— spasticity
<i>Batulinum</i> toxin	Decrease in neurotransmitter (acetylcholine) release from neurons (floccid paralysis)
<i>Heat labile</i> toxin of <i>ETEC</i> and <i>Cholera</i> toxin (<i>V. cholerae</i>)	Activation of adenylate cyclase , ↑ cAMP in target cells—secretory diarrhea
<i>Heat stable</i> toxin	↑ cGMP in target cells—secretory diarrhea
<i>Verocytotoxin</i> (EHEC) and <i>Shiga</i> toxin (<i>Shigella dysenteriae</i> type 1)	Inhibit protein synthesis by inhibiting ribosome

Bacterial Division

- Bacteria divide by **binary fission** where one bacterium enlarges and divides into two daughter cells. Nuclear division precedes cell division.
- The interval between two cell divisions or the time required for a bacterium to give rise to two daughter cells under optimum conditions is known as the **generation time** or **doubling time**.

Contd...

Generation times (doubling time)

- Coliforms-20 minutes
- Tubercle bacilli-14 hours
- Lepra bacillus-12 to 13 days

Bacterial Count

- Total count** is the total number of bacteria present in a specimen irrespective of whether they are living or dead
- Viable count**: measures only viable (living) cells which are capable of growing and producing a colony on a suitable medium.

Bacterial Growth Curve

- Lag Phase**: NO increase in cell number; **increase in cell size** occurs.
- Log (logarithmic) phase**: Exponential (geometric) **increase in cell division** and cell number (1 to 2, 4 to 8 and so on); bacterial cells are small and **uniformly stained**. If the logarithm of the viable count is plotted against time, a **straight line** will be obtained.
- Stationary phase**: Cell division **stops**; growth curve becomes **horizontal**. **Sporulation, exotoxin production** and **antibiotic production** occur during this phase.
- Decline (death) phase**: bacterial population **decreases** due to cell death.

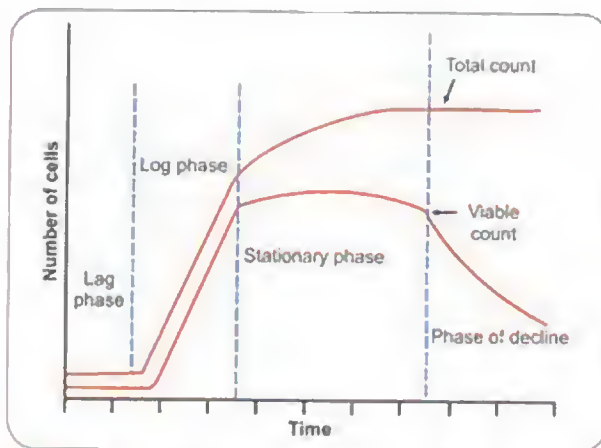


Fig. 5.8: Bacterial growth curve. The viable count shows lag, log, stationary and decline phases. In the total count, the phase of decline is not evident

Temperature and Bacterial Growth

Type of bacteria	Optimum temperature
Mesophilic (moderate temperature loving; most pathogenic bacteria)	20–40°C

Contd...

Contd...

Type of bacteria	Optimum temperature
Psychrophilic (cold loving; soil and water saprophytes)	0–20°C
Thermophilic (heat loving; Bacillus stearothermophilus)	50–60°C

Oxygen and Bacterial Growth

- Aerobic bacteria**: require oxygen for growth:
 - Obligate aerobes**: Can grow only in compulsory presence of oxygen (*V. cholerae*).
 - Facultative anaerobes**: Ordinarily aerobic but can also grow in the absence of oxygen, although less abundantly (*E. coli*; most bacteria of medical importance)
 - Microaerophilic**: Organisms grow best at low concentration of oxygen (5%)—*Campylobacter* spp.
- Obligate anaerobes**: can grow only in the absence of oxygen:
 - Actinomyces*, *Bacteroides*, and *Clostridium* ('ABC are Anaerobes').
 - Anaerobes are **normal flora in GI tract, pathogenic elsewhere**.
 - Aminoglycosides** are **ineffective** against anaerobes because these antibiotics require O_2 to enter into bacterial cell.
 - They **lack catalase and/or superoxide dismutase** and are thus susceptible to oxidative damage.
 - Generally foul smelling** (short-chain fatty acids), are difficult to culture, and produce gas in tissue.

Carbon Dioxide and Bacterial Growth

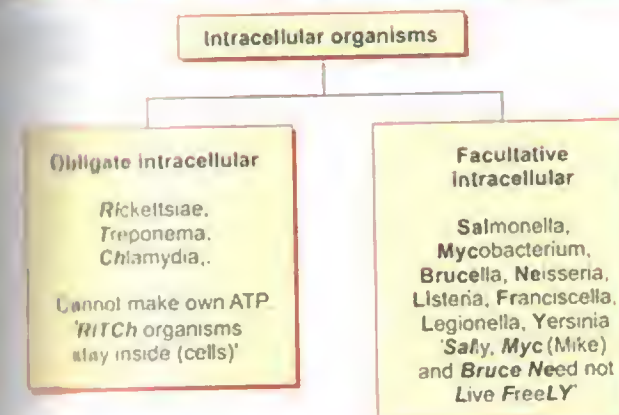
- Bacteria that grow well in the presence of high levels of CO_2 (5–10%) are called **capnophilic** bacteria; e.g. *Brucella abortus*, *H. influenza*, etc.

pH and Bacterial Growth

- Most pathogenic bacteria grow best at neutral or slightly alkaline pH (7.2–7.6).
- Bacteria growing at **acidic** pH (4.0) = *Lactobacillus*.
- Bacteria growing at **alkaline** pH (8.2–8.9) = *V. cholerae*.

Special bacterial growth factors

- Salmonella Typhi*—Tryptophan
- Gonococci*—Glutathione
- H. influenzae*—factors V and X



MICROSCOPES

- Light microscope** (uses visible light as source of illumination)
 - Brightfield microscopy**:
 - Aka **compound light microscope** or **optical microscope**; MC used microscope in labs.
 - Course of light = Light source/illuminator > condenser > specimen > objective lenses > eyepiece.
 - Objective lenses commonly used are low power (10X); high power (40X) and oil immersion (100X).
 - Size of medically important bacteria: 2–5 μ length X 0.2–1.5 μ width.
 - Darkfield microscopy**:
 - Aka **dark ground microscope**: **reflected light** is used instead of transmitted light using a 'dark field condenser'.
 - Useful for demonstrating very thin bacteria—*Spirochetes (T. pallidum)* and for visualizing **flagella**.
 - Phase contrast microscope**:
 - This improves contrast and makes evident the structures within the cells that differ in **thickness or refractive index**.
 - Used to study unstained living cells and internal structures of cells.
 - Interference microscope**:
 - This **reveals cell organelle** and also enables **quantitative measurement of chemical constituents** of cells such as **lipids, proteins and nucleic acids**.
 - Polarization microscope**:
 - This enables the study of intercellular structures using **differences in birefringence**.

2. UV rays as source of illumination

➤ Fluorescent microscopy:

- Tissues are stained with **fluorescent dye** (**auramine, rhodamine, lissamine**) and are examined under microscope with UV light—they become luminous and are seen as bright objects against a dark background.

3. Laser as source of illumination

➤ Confocal microscopy:

- This is like a **miniature CT scan** for the cells.

4. Electron beam forms image of specimen

➤ Electron microscopy:

- This uses **electromagnetic lenses**, electrons and a fluorescent screen to produce the magnified image.
- Two types are **Transmission** and **Scanning** electron microscopy.

5. Scanning probe microscopes:

- Maps the bumps and valleys of a surface on an atomic scale. Resolving power is **more than** electron microscope; no special preparation of specimen is required.
- Examples are **Scanning tunneling microscopes** and **Atomic force microscope**.

Resolving powers

➤ Naked eye	: 0.2 mm (200 microns)
➤ Light microscope	: 200 nm (0.2 microns)
➤ Electron microscope	: 0.1 nm

STAINING TECHNIQUES

Simple Stains

- Methylene blue** and **Basic fuchsin**.

Negative Staining

- Here the background is stained and the **structure to be identified is not stained**.
- India Ink** and **Nigrosin** are used commonly.
- Used to demonstrate **bacterial capsule** and **cryptococcus**.

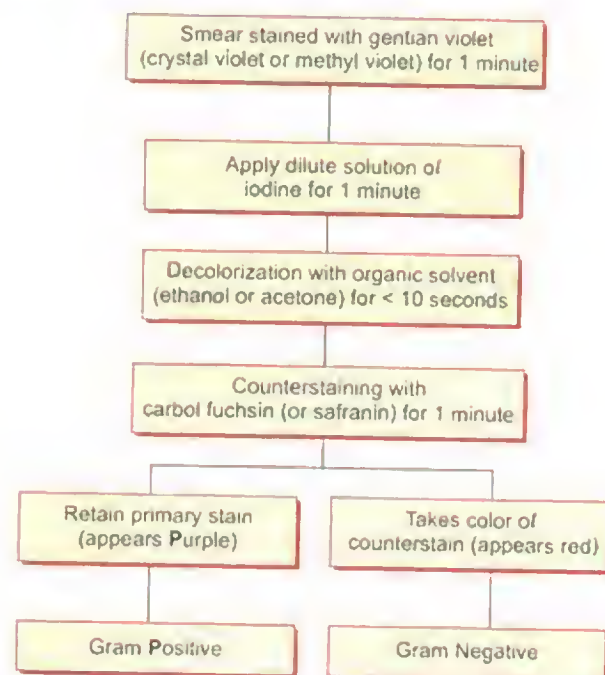
Impregnation Staining

- Silver impregnation** renders the organism that is very slender to be visualized; used for *Treponema*, *Borrelia* and *Leptospirae*.

Differential Stains

- Gram stain and acid fast stains.

Gram Staining



Organisms that do not gram stain well

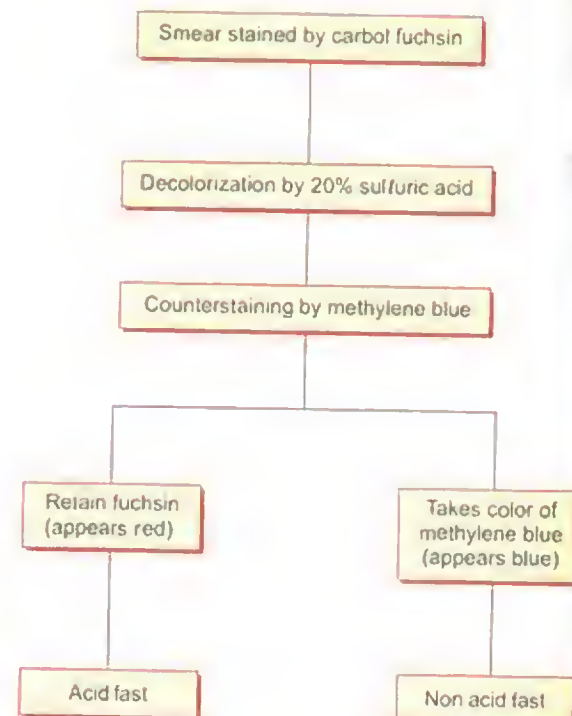
- Treponema* (too thin to be visualized). Require **darkfield microscopy** and fluorescent antibody staining.
 - Rickettsia* (intracellular parasite).
 - Mycobacteria* (high-lipid-content cell wall) requires acid-fast stain.
 - Mycoplasma* (no cell wall).
 - Legionella pneumophila* (primarily intracellular), **silver stain**.
 - Chlamydia* (intracellular parasite; **lacks** muramic acid in cell wall).
- 'These Rascals May Microscopically Lack Color'

Acid Fast Staining

- MC used method is modified Ziehl Nielsen staining.
- Acid fastness depends upon mycolic acid and integrity of cell wall.
- M. leprae* is less acid fast than *M. tuberculosis*. Hence 5% sulfuric acid instead of 20% is used for decolorizing after staining with carbol fuchsin.

Acid fast organisms

- All mycobacteria: *M. tuberculosis*, *M. leprae*, *M. bovis*, atypical mycobacteria.
- Nocardia asteroides*, *Legionella micdadei*, *Rhodococcus*
- Bacterial **spores** and **sperm** head.
- Oocysts of *Cryptosporidium*, *Cyclospora*, *Isospora*
- Tinea saginata* egg and scolex
- Hooklets** of hydatid cyst and *S. mansoni* eggs.

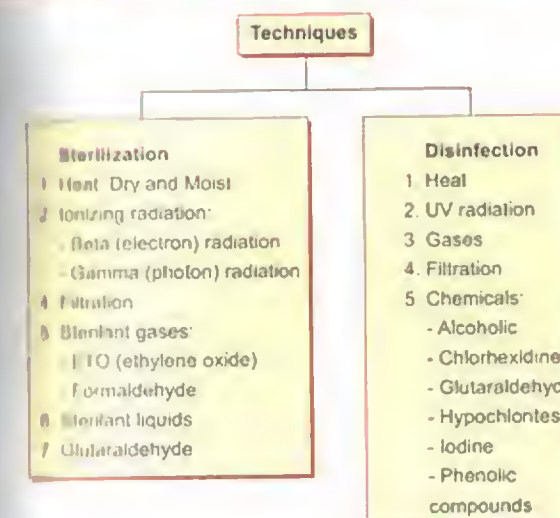


Special staining methods

- Spore** staining: Acid fast stain (0.25% H_2SO_4) and Schaffer and Fulton method
- Lipids**: stained by Sudan Black stain
- Carbohydrates** stained by: Iodine stain
- Flagellar** stain: tannic acid (Leifson method)

STERILIZATION

- Sterilization** is the process by which an article or medium is freed of **ALL** living microorganism either in the vegetative state or spore state.
- Disinfection** means destruction or removal of **all** pathogenic organisms (not sporicidal).
- Antiseptics**: Disinfectants that can be safely applied to skin or mucus membrane are called antiseptics or skin disinfectants-MC used is **povidone iodine**; others are **chlorhexidine** and **isopropyl alcohol**.



Dry Heat

- Flaming** (for loop or wire tip of forceps or spatulas)
- Flaming or incineration**: contaminated cloth, animal carcasses; pathological materials, PVC and polythene.
- Hot air oven**: Most widely used method of sterilization by dry heat. It is used to sterilize glassware, scalpels, all glass syringes, liquid paraffins, dusting powder, fats, oils, glycerol and grease.

Moist Heat

- Temperature below 100 °C**
 - Pasteurization** of milk:
 - Holder method 63 °C for 30 minutes
 - Flash method 72 °C for 15-20 seconds
 - Coxiella burnetii* may survive the holder method.
 - Other methods:
 - Vaccine bath given for 1 hour at 60 °C for bacterial vaccines.
 - LI media and Loeffler's slope are sterilized by heating at 80 °C for 30 minutes for 3 successive days in inspissator.
- Temperature at 100 °C**
 - Boiling at 100 °C for 10 minutes will kill bacteria but NOT spores and viruses.
- Steam at atmospheric pressure**
 - Heating at 100 °C for 20 minutes on three successive days—**intermittent sterilization** or **tyndallization**: used for sterilizing culture media.
- Steam under pressure**
 - Autoclave** (steam sterilizer) usually done at 121 °C for 15 minutes.
 - Most effective sterilizing agent for dressings, instruments, lab wares.
 - Autoclave kills spores effectively.

- Sterilization control is by (1) Biological = filter paper strip impregnated with 106 spores of *Bacillus stearothermophilus*; (2) Chemical = **Browne's tube** containing red solution changes to green when autoclaving is successful. (3) thermocouples.

Aldehydes

1. Formaldehyde

- Formaldehyde is **bactericidal**, **virucidal** and **sporicidal**.
- Available as **formalin** (37% formaldehyde) and **formaldehyde gas** (generated by adding $KMnO_4$ to formalin).
- Formaldehyde is used for:
 - Preserving anatomic specimens (formalin)
 - Fumigation of wards, OT, sick rooms and labs (gas)
 - Disinfection of membranes in dialysis equipment.

2. Glutaraldehyde

- About 2% glutaraldehyde (cidex) effective against all microorganism including spores (slow action).
- Used for sterilization of **fiber optic endoscopes** (**bronchoscope**, **cystoscopes**) and **lenses**.

Ethylene Oxide (ETO)

- Colorless gas** with **sweet ethereal smell**.
- Highly **inflammable**-hence not used in fumigating rooms.
- Boiling point is 10.7 °C.
- Used to sterilize **heat sensitive articles-heart lung machine, respirators**, sutures, **dental** equipment, books and clothing.
- In ETO sterilization there are 2 cycles-**cold cycle** (at 37 ± 5 °C) and **hot cycle** (54 ± 5 °C).
- In these cycles the relative humidity is maintained at **40-50%** and ETO concentration at **700 mg/L**.
- ETO is effective against **all microorganisms including spores**.

Alcohols

- Commonly used are **ethyl alcohol** (ethanol) and **isopropyl alcohol**.
- NOT effective **against viruses and spores**, BUT **HIV is susceptible** to ethyl alcohol (70%) and isopropyl alcohol (35%) in absence of organic matter.
- Act by **denaturing bacterial proteins**.
- They must be used at 60-70% concentration mixed with water to be effective.
- Used as surface disinfectants (**alcohol wipes**) and for disinfecting **thermometers**.

Halogens

- Bactericidal, virucidal and sporicidal.
- Chlorine and iodine are used.
- Chlorine used as *chlorine tablets* or *sodium hypochlorite*.
- *Chlorine* commonly used for disinfection of water and disinfection of *equipment soiled with blood and blood spills in wards/OT* (in form of *sodium hypochlorite*).
- *Iodophores* are compounds of iodine with non-ionic wetting or surface active agents-MC example is *povidone iodine*—a compound of *polyvinylpyrrolidone* with iodine.
- Iodophors retain the germicidal efficacy of iodine but unlike iodine generally are *nonstaining and relatively free of toxicity and irritancy*.
- Povidone-iodine is MC used a *skin disinfectant*.

Radiations

- *Gamma radiation* (ionizing) used for sterilization of *packaged disposable articles* such as *catgut, plastic syringes, IV lines, catheters* and *gloves* that cannot withstand heat.
- There is no appreciable increase in temperature in this method, hence called '*cold sterilization*'.
- *UV radiation* (non-ionizing) used for entry ways, OT's and laboratories.

Testing of disinfectants

- *Phenol co-efficient* test
 - Rideal Walker test
 - Chick Martin test
- Minimum Inhibitory Concentration (MIC)
- Kelsey Sykes test (Capacity test)
- In-use test (Kelsey and Maurer)

Classification of Disinfectants

Level	Definition	Examples
High	Destroys all microorganisms (including mycobacteria) and 'some' spores	Glutaraldehyde, hydrogen peroxide, hypochlorites, peracetic acid, ethylene oxide
Medium/Intermediate	Destroys bacteria including mycobacteria, most fungi and viruses; NOT sporicidal	Alcohol, iodophors, phenolic compounds
Low	Destroys bacteria, some fungi and viruses; NOT tuberculocidal or sporicidal	Quaternary ammonium compounds, cetrimide, benzalkonium chloride)

Spaulding Classification of Sterilization

Device classification	Device examples	Level of disinfection
Critical equipment (enters sterile tissue or vascular system)	Implants, scalpels, needles, other surgical instruments	Sterilization; sporicidal chemical with prolonged contact
Semicritical (touches mucus membranes and intact skin; except dental)	Laryngoscopes, endoscopes, vaginal speculum	High level disinfection
Noncritical equipment (touches only intact skin and NOT mucus membranes)	Stethoscopes, ECG electrodes; BP cuffs; electronic thermometers, bedpans)	Intermediate and low level disinfection

Disinfection of Spores (Sporicidal Agents)

- 'EFGH': Ethylene oxide; Formaldehyde; Glutaraldehyde; Halogens
- 'POOP': Peracetic acid, O-Phthalic acid, Ozone, beta Propiolactone
- *Plasma* sterilization, *autoclave* and *hot air oven*.

Disinfection of Sputum

- *Burning* is best.
- Others are *boiling; autoclaving; 5% cresol*.

Order of Resistance to Disinfectants

Prions (most resistant) > Bacterial spores > Mycobacteria > Non-enveloped/Non lipid virus > Gram negative bacteria > Fungi > Gram Positive bacteria > Enveloped/Lipid virus.

Sterilization of prions

- Wet heat: *Autoclave* at 134–138 °C for 1 hour.
- Chemicals: Prions are inactivated by
 - *Sodium hypochlorite* (25% available chlorine) for 1 hour; *Phenol* (90%); Household bleach; *Ether*; *Acetone*; *Urea* (6 mMol/L); *Sodium dodecyl sulfate* (10%); *Iodine*
- *NOT effective* agents: dry heat, aldehydes, ETO and ionizing radiation.

Summary of Sterilization Methods in Different Situations

Material	Method of sterilization/ disinfection
Paraffin, glass syringe, flask, slide, oil, grease, fat, glycerol	Hot air oven

Contd...

Special Media

- They have added ingredients for special purpose or for bringing out certain characteristics or providing special nutrients required for growth of the bacterium under study. Examples in table are as follows.

Media	Example
Enriched media (when basal medium is added with nutrients such as blood, serum or egg)	<ul style="list-style-type: none">• <i>Blood agar</i> (blood + nutrient agar) – for growth of streptococcus• <i>Chocolate agar</i> (heated blood agar) – for isolation of <i>Nelisseria</i> and <i>H influenzae</i>• <i>Loeffler's serum slope</i> – for grouping <i>C diphtheriae</i>
Enrichment media (contains substances in liquid medium which have stimulating effect on the bacteria to be grown or inhibits its competitors)	<ul style="list-style-type: none">• <i>Tetrothionate</i> broth – allows typhoid and paratyphoid bacilli to grow• <i>Selenite F</i> broth – similar to above• <i>Alkaline peptone water</i> – to grow vibrio cholerae
Selective media (contain substances that inhibit all but a few types of bacteria and facilitate the isolation of a particular species)	<ul style="list-style-type: none">• <i>Deoxycholate citrate agar</i> – for enteric bacilli – <i>shigella</i> and <i>salmonella</i>• <i>Bile salt agar</i> – vibrio cholerae• L-J medium for <i>Mycobacterium TB</i>
Differential media (medium contains substances that help to distinguish differing characteristics of bacteria)	<ul style="list-style-type: none">• <i>MacConkey's medium</i> – to differentiate lactose and non-lactose fermenters
Indicator media (contain an indicator which changes color when a bacterium grows on them)	<ul style="list-style-type: none">• <i>Wilson Blair sulfite medium</i> – <i>S typhi</i>• <i>MacConkey's agar</i>

Material	Method of sterilization/ disinfection
Small thermometer	Isopropyl alcohol
Entryway, ward, laboratory	Formaldehyde gas > UV
Preservation of anatomical specimen	
Bed linen blanket	
Endoscope, bronchoscope, fiberoptic scopes	Glutaraldehyde 2% (cidex)
Ventilating machine, respirator, dental equipments	Ethylene oxide
Antibiotic, sera, antibiotic, sugar solution, body fluids	Filtration
Surgical instruments	Cresol
Milk	Pasteurization
Plastic syringe, catgut suture, swab, catheter, bone and tissue grafts, adhesive dressings, gloves	Ionizing radiation
Culture media, surgical metal instruments, glassware and culture materials except catgut	Autoclave
Metallic inoculation wire	Red hot flame by Bunsen burner
Infected solid dressings, bedding and animal carcasses	Incineration (burning)
Water	Chlorine as sodium hypochlorite 0.2%
Skin	Tincture iodine, spirit (70% ethanol), savlon
Contact lenses	Hydrogen peroxide

CULTURE MEDIA

Simple (Basal) Media

- This is simple with no added ingredients.
- *Nutrient broth* is a simple liquid medium that consist of *peptone, meat extract, sodium chloride and water*.
- *Nutrient agar* is a simple solid medium; it is prepared by adding 2% *agar* to the nutrient broth; it is the *simplest and MC used medium* in microbiology.

Complex Media

- Media that contain some ingredients of unknown chemical composition are complex media; one common ingredient is *peptone*.

Agar Agar or Agar

- Agar is obtained from sea weeds and is universally used for preparation of solid media.
- Agar has melting point of 95 °C and hence preferred over gelatin (melting point < 35 °C).
- Agar has NO nutritive value.

Blood Culture

- Majority of blood culture media *bottles* contain *sodium polyanethol sulfonate (SPS)*—a polyanionic *anticoagulant*.
- Blood specimens of 5–10 ml. are added to bottles containing 50–100 ml. of medium to achieve a *1:10 blood:medium ratio*.

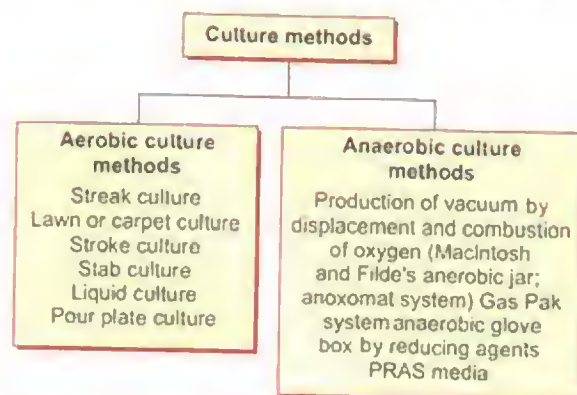
- The bottles are **incubated at 37 °C**; subcultures are done after 24 hrs, 96 hrs and 14 days at 37 °C.

Culture media for anaerobic bacteria

- Robertson's cooked meat medium
- Smith-Noguchi medium
- Thioglycollate broth
- Heating and subsequent plating method.

More One-Liners

- Microbiology and virology samples collected in **formalin are unacceptable** for culture.
- In a patient with UTI, **CLED** (Cystine, Lactose, Electrolyte Deficient) media is preferred over McConkey's media because it supports growth of certain staphylococcus, streptococci and candida strain.
- Sabouraud's dextrose agar (**SDA**) is the MC used medium for fungal culture; its **pH is adjusted to 5.4**.



BACTERIAL GENETICS

Plasmids

- Plasmids are extrachromosomal circular dsDNA molecules that exist in the free state in the cytoplasm of bacteria and also found in some yeasts
- Not essential for life** (bacteria may gain or lose plasmid during their lifetime)
- May be present **singly or in multiple numbers** (upto 40 per cell)
- Capable of **replicating independently**
- Plasmid may integrate with chromosomal DNA of bacteria and such plasmids are called **episomes**
- The process of eliminating the plasmids from bacteria is called **curing**.

Classification of Plasmids

- Compatible and incompatible plasmids (can or cannot stay together inside a cell)

- Conjugative and non-conjugative plasmids (can or cannot self transfer themselves)
- Based on function:
 - Fertility (F) plasmids
 - Resistance (R) plasmids
 - Col plasmids (code for bacteriocins)
 - Virulence plasmids (codes for toxins, adhesins, etc.)
 - Metabolic plasmids
- Plasmid as a vector (in gene therapy).

Transfer of Genetic Material in Bacteria

1. Horizontal (lateral) gene transfer:

- A process by which genetic material is passed between **two different organisms** of the **same generation** maybe even between organism of different species (plant to microbe).
- The recipient is **NOT** the offspring or donor.
- Most important example is gene transfer between the bacteria.
- The process of horizontal gene transfer in bacteria are **conjugation, transduction** and **transformation**.
- Artificial horizontal gene transfer is used in **genetic engineering**.

2. Vertical gene transfer:

- Transmission of genes from the **parental generation to offspring** via sexual or asexual reproduction.

Transformation

- Transfer of genetic information through the '**free**'/'**naked**' DNA.
- It was first demonstrated by **Griffith** in **Streptococcus pneumoniae** in 1928.
- This was the **first example of horizontal gene transfer** to have been discovered.

Transduction

- Transfer of a portion of DNA from one bacterium to another by a **bacteriophage**.
- Bacteriophages are viruses that parasitize bacteria and consist of a nucleic acid and protein coat.
- Transduction may be:
 - Generalized**: When it involves any segment of donor DNA.
 - Restricted**: When a specific bacteriophage transduces only a particular genetic trait (e.g. **prophage lambda** in **E coli K12**: 'Gal+' gene determines fermentation of galactose).
- The plasmids determining **penicillin resistance** in **staphylococci** are transferred from cell to cell by transduction.

Transduction is the **most widespread mechanism** of gene transfer among prokaryotes.

Lysogenic Conversion

- Bacteriophages exhibit two types of lifecycle:
 - Virulent or lytic cycle**: Large number of progeny phages are built up inside the host bacterium which ruptures to release them.
 - Temperate or nonlytic cycle**: Host bacterium is unharmed; phage DNA becomes integrated with bacterial chromosome as the **prophage** and is transferred to daughter cells. This process is called **lysogenic conversion**.

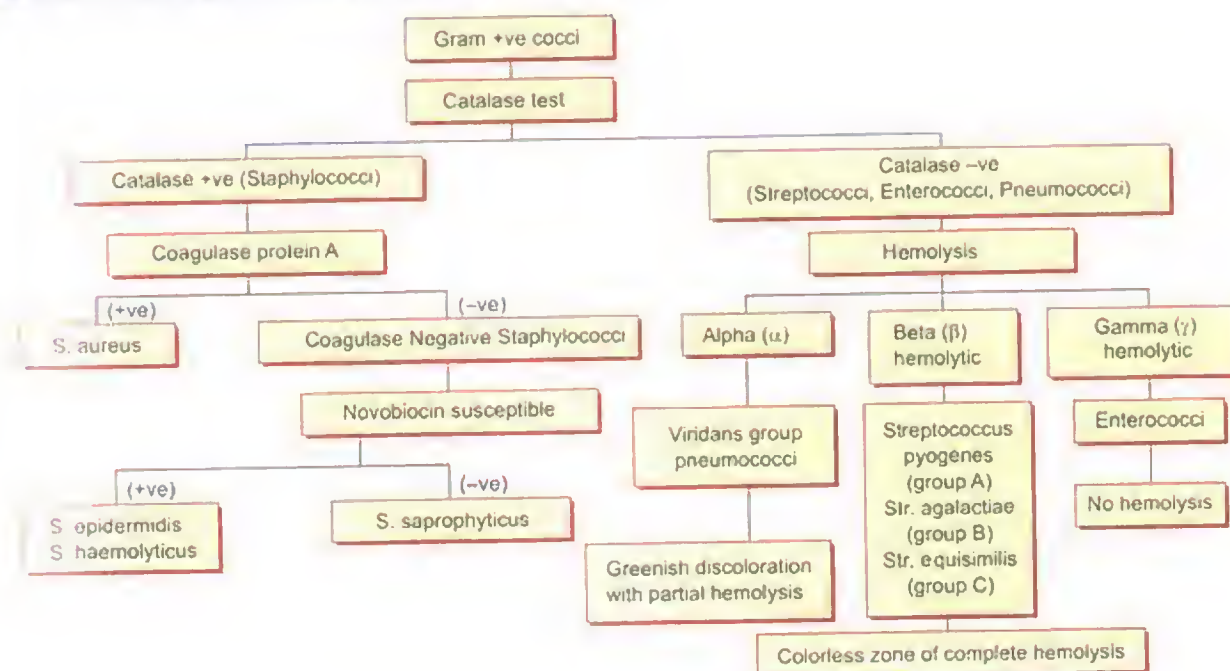
Bacteria which acquire toxicity through lysogenic conversions are 'ABCDE'

- A** and **C** of Streptococcal pyrogenic exotoxin
- B**otulinum toxin; **C** and **D**
- C**holera toxin
- D**iphtheria toxin (through **phage beta**) and **E** coli (verocytotoxin).

Conjugation

- The donor or male cell, makes contact with another, the recipient or female cell, and **DNA is transferred directly** from donor to recipient through **conjugation tube (sex pilus)**.

Classification of Gram Positive Cocci (see Flowchart)



- Lederburg and Tatum** (1946) first described bacterial conjugation in a strain of **E coli K12**.
- Medically important factors transmitted by conjugation are
 - Coliciniogenic (col) factor**
 - Resistance factor (R) plasmids**—codes for transferable **multiple drug resistance**.

Transposons

- Certain structurally and genetically discrete segments of DNA which move around between chromosomal and extra chromosomal DNA molecules within cells are called '**transposons**' ('**jumping genes**').
- Barbara McClintock** discovered transposons in corn for which she was awarded the Nobel prize in medicine in 1953.

Few firsts

- First example of **gene transfer by transformation**: **Pneumococci**
- First example of **restricted transduction**: **E coli**
- First example of **lysogenic conversion**: **C diphtheriae**
- First example of **conjugation**: **E coli K12**
- First example of **transferable drug resistance**: **Shigella**

Drug Resistance

Mechanisms of Antimicrobial Drug Resistance

- Decreased permeability of drugs across the cell wall
- Efflux pumps (mediate expulsion of drugs from the cell soon after their entry)
- By modification of the antimicrobial target sites within the bacteria
- By enzymatic inactivation of antimicrobial drug.

Beta Lactamase Enzymes

- Beta lactamase enzymes are capable of hydrolysing the beta lactam ring of antibiotics thereby inactivating their antibacterial properties.
- It is observed in **both** gram positive and gram negative bacteria.
- They are **plasmid coded**, and transferred from one bacterium to another by **mostly by conjugation** (except in *Staphylococcus* where they are transferred by **transduction**).
- Extended spectrum beta lactamases (**ESBL**) can **degrade 1st, 2nd and 3rd generation cephalosporins** and **monobactams**; BUT remain **sensitive to carbapenems** (imipenem, ertapenem, doripenem and meropenem).
- The ESBL that *E coli* MC produce are called **CTX-M** enzymes.
- Beta lactamases can be classified by two ways:
 - **Ambler** classification (**structural** or **molecular** classification based on amino acid similarity)
 - **Bush-Jacoby-Medeiros** classification (**functional/phenotypic** classification).

Antimicrobial susceptibility testing methods

- **Disk diffusion** methods (Kirby-Bauer and Stokes methods; MHA-Mueller Hinton Agar is considered best medium)
- **Dilution tests** (**Broth and agar** dilution can calculate **MIC**, (Minimum Inhibitory Concentration))
- **Epsilometer** (E test)-can calculate **MIC**
- Automated methods (VITEK 2; Phoenix system)
- Molecular methods (**PCR** detecting drug resistant genes, e.g. *MecA* gene for MRSA)

STAPHYLOCOCCUS AUREUS

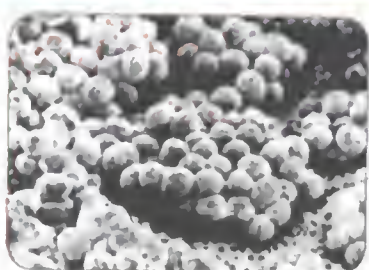


Fig. 5.9: Colonies of *Staphylococcus aureus* (electron microscopic)

Epidemiology

- S aureus* is part of normal human flora.
- The **anterior nares** are the **MC site** of human colonisation. **30%** of general population are **nasal carriers**.
- Skin, vagina, axilla, nasopharynx and perineum are all colonized.
- MC source of infection** is **endogenous infection** from individuals **own colonizing strains**.
- MC method of transmission** of *Staphylococci* in **hospital** is by **contaminated hands**. **Hand washing** is the most effective method of preventing hospital cross infection.
- Overall **30-40% strains** of *S aureus* are **MRSA**.
- Methicillin resistance** is expressed **more at 30 °C** than 37 °C.

Culture characteristics

- **Gram + cocci** in **grape like clusters**
- Colonies have **golden color**
- **Oil paint** appearance on nutrient agar
- Addition of **10% NaCl** makes media selective for *Staphylococci*
- Selective media:
 - **Ludiam's** medium (lithium chloride and tellurite)
 - **Mannitol salt** agar
 - **Salt milk** agar
- On blood agar there is **beta hemolysis**.

Biochemical Identification

- Catalase +ve**
- Coagulase +ve**
- Phosphatase +ve**
- Ferments **mannitol**
- Hydrolyse urea (**Urease +ve**)
- Produce **thermonuclease enzymes (DNAase)**
- Sensitive to Lysostaphin**
- Methyl red and Voges Proskauer test **+ve**; reduces nitrates to nitrites; liquefy gelatin.

Virulence Factors

- Enterotoxin:**
 - **Preformed exotoxin**—secreted in the intestines.
 - **Type A MC**.
 - **Heat resistant** (not destroyed by heating food).
 - Causes **food poisoning** typified by **vomiting and diarrhea within 1-6 hours** of food consumption.
 - It **stimulates the vagus nerve** and **vomiting center** of the brain.
 - **Self limiting**; **NO antibiotics** required.

Toxic shock syndrome toxin 1 (TSST 1)

- Also **enterotoxin** For **pyrogenic exotoxin C**.
- A **superantigen** causing **unregulated inflammation**.
- Acquired from **contaminated tampons** in **menstruating women** (rare now) or from infected wounds (accounts for 50% cases); leads to **Toxic shock syndrome**—signs are **systemic hypotension, tachycardia**, high fever, vomiting/diarrhea, **headache**, sunburn like **rash**, muscle aches; redness of eyes and throat
- In staphylococcal TSS **bacteremia is rare**; BUT **rash is common** (opposite is seen in streptococcal TSS).
- Treatment: **Clindamycin**.

Exfoliative toxin:

- Also **exfoliatin** or **epidermolytic toxin**.
- Another **superantigen** that causes **Staphylococcal Scalded Skin Syndrome (SSSS)**.
- SSSS in neonates is called **Ritter's disease** and in older individuals is called **toxic epidermal necrolysis**.
- Diffuse tender erythema often with bullae and desquamation. **Nikolsky sign** is present.
- Milder and more common forms of SSSS include **pemphigus neonatorum** and **bullous impetigo**.

Protein A:

- Basis of **coagglutination reaction**.
- Binds to **Fc** portion of **IgG** leaving **Fab** region free to bind antigen.

Hemolysins:

- **Alpha hemolysin**: inactivated at 70 °C; **paradoxically reactivated** at 100 °C.
- **Beta hemolysin** is a **sphingomyelinase**; it exhibits **hot-cold** phenomenon.

Leukocidins:

- **Panton-Valentine toxin**
- Important in **MRSA infection**
- **Synergohymenotropic toxin** (biocomponent toxin like **gamma hemolysin + leukocidins**).
- Others are **gamma** and **delta hemolysin**; **clumping factor** (responsible for **slide coagulase test**).

Typing of S Aureus

- MC method of typing-Phage typing**
- National center for Phage typing**: Maulana Azad Medical College (MAMC), New Delhi
- Epidemic strain** of *S aureus* is **Phage type 80/81**. It causes outbreaks in hospitals (hence called **hospital strains**).

Tube coagulase	Slide coagulase
Due to coagulase enzyme	Due to clumping factor
Requires CRF in plasma	Does not require CRF in plasma
Test +ve: coagulum formed/ plasma clotted	Test +ve: clumps formed

- Both slide and tube coagulase +ve: *S. aureus*; *S. hyicus* and *S. intermedius*
- Only **SLide** coagulase +ve: *S. lugdunensis*
- Only tube coagulase +ve: *S. schleiferi*.

S aureus is the MC cause of following conditions

- **Skin and soft tissue disease:**
 - Furuncles (boils); carbuncles; folliculitis; bullous impetigo; botryomycosis (mycetoma like condition with multiple discharging sinuses); acute paronychia; surgical wound infection; mastitis and breast abscess (in nursing mothers); postoperative parotitis; epidural abscess; tropical myositis.
- **Musculoskeletal disease:**
 - Osteomyelitis and septic arthritis in native joints
- **Respiratory:**
 - Pneumatoceles; post-influenza pneumonia
- **Toxin mediated diseases:**
 - Toxic shock syndrome (TSS); food poisoning; scalded skin syndrome (SSS); toxic epidermal necrolysis (TEN).
- **Heart:**
 - Acute infective endocarditis (in native valves)
 - Endocarditis in IV drug abusers.

Treatment of S Aureus Infections

- Sensitive to penicillin: Penicillin G
- Sensitive to methicillin: Nafcillin or oxacillin (**Methicillin caused interstitial nephritis and no longer available!**)
- For **MRSA** (**Methicillin Resistant Staphylococcus Aureus**):
 - **Vancomycin** is **DOC**.
 - Alternatives are daptomycin, linezolid or ceftaroline (all beta lactam drugs should be avoided except 5th generation cephalosporins)
 - **DOC** for nasal carriers of MRSA-2% mupirocin ointment.
- For **VRSA** (**Vancomycin Resistant Staphylococcus Aureus**) or **VISA** (**Vancomycin Intermediate Staphylococcus aureus**) alternatives are:
 - Daptomycin is **DOC**
 - Alternatives are **dalbavancin/telavancin** (derivatives of vancomycin); **linezolid/tedizolid**; **ceftaroline**, **quinupristin/dalfopristin** (parenteral streptogramin antibiotic).

Drug Resistance in S Aureus

Mechanisms are:

1. **Production of beta lactamase enzyme:** Beta lactamase production is controlled by **plasmid**; plasmid is transmitted and acquired mainly by **transduction** (drug resistance in *Staphylococcus* is by **transduction**)
2. Alterations of **surface receptors**: It is the **major mechanism of methicillin resistance**; MRSA strains carry an extra gene (**mecA**) that **encodes an altered penicillin binding protein** (called **PBP2a**). PBP2a production is chromosomally mediated.

COAGULASE NEGATIVE STAPHYLOCOCCI (CONS)

<i>Staphylococcus epidermidis</i>	<i>Staphylococcus saprophyticus</i>
Most common CONS	
Catalase positive	Catalase positive
Novobiocin sensitive ('Your epidermis (skin) is sensitive, right?')	Novobiocin resistant
Causes – Prosthetic device infections (valves, shunts, stitch abscesses) Bacteremia, nosocomial infections via Indwelling catheters (Foley's catheter, Central venous Catheter) Prosthetic valve Endocarditis , within 12 months of replacement	Causes – UTI in young women
Virulence by plastic adhesins; produces polysaccharide glycocalyx (slime, Biofilm production)	Virulence by mucosal adhesins

MICROCOCCI

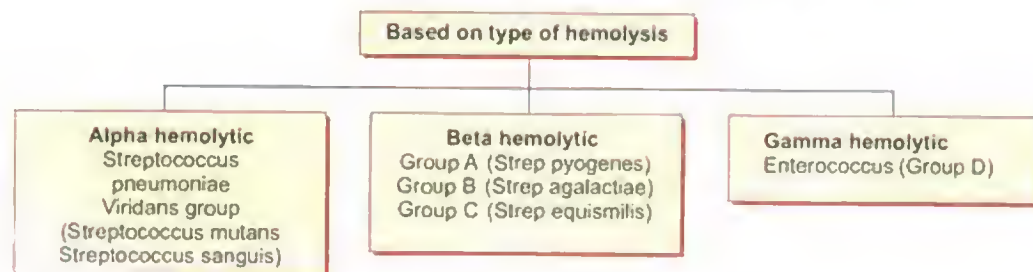
- **Gram positive** cocci arranged in **pair, tetrads or clusters**
- **Catalase and oxidase positive**; **Obligate aerobes**.
- Usually **non-pathogenic** and are parasites on mammalian skin.
- **Hugh Leifson's oxidation fermentation test** is used to **differentiate staphylococci and micrococci**; micrococci show oxidative and staphylococci show fermentative patterns.

HEMOLYTIC BACTERIA

α-hemolytic bacteria	Form green ring of partial hemolysis around colonies on blood agar. Includes: <ul style="list-style-type: none"> • <i>Streptococcus pneumoniae</i> (catalase -ve and optochin sensitive) • <i>Streptococcus viridans</i> (catalase -ve and optochin resistant)
β-hemolytic bacteria	Form complete clear/colorless area of hemolysis on blood agar. Includes: <ul style="list-style-type: none"> • <i>Staphylococcus aureus</i> (catalase and coagulase +ve) • <i>Streptococcus pyogenes</i> – group A strep (catalase -ve and bacitracin sensitive) • <i>Streptococcus agalactiae</i> – group B strep (catalase -ve and bacitracin resistant) • <i>Listeria monocytogenes</i> (tumbling motility, meningitis in newborns, unpasteurized milk)
γ-hemolytic bacteria	A misnomer since there is actually NO hemolysis: <ul style="list-style-type: none"> • Enterococcus

CLASSIFICATION OF STREPTOCOCCI (SEE FLOWCHART)

- **Lancefield system:** Based on **carbohydrate antigens** in **cell wall** of the bacteria, the **β-hemolytic streptococci** can be classified into **20 Lancefield serogroups A to V** (except I and J).
- Group A Streptococcus (GAS, *Streptococcus pyogenes*) is further subclassified:



Staphylococcus Hemolyticus

- The 2nd most Important CONS after *Staph. epidermidis*.
- It has **highest level of antibiotic resistance among the CONS**.

- ▶ Based on the **M protein** into >100 **Griffith types** (1, 2, 3, etc.)
- ▶ Imm typing based on the gene coding for M protein, 124 imm genotypes are identified.

STREPTOCOCCUS PYOGENES (GROUP A STREPTOCOCCI)

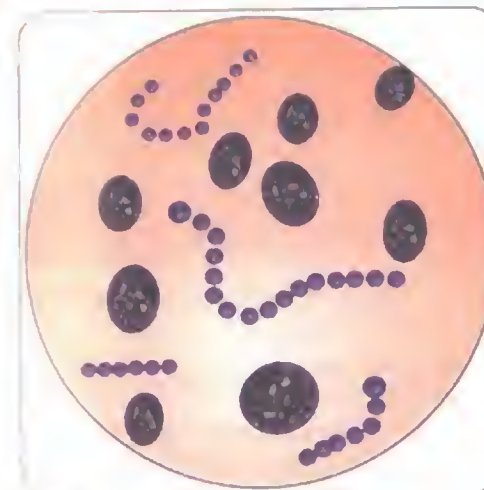


Fig. 5.10: Streptococcus

Biochemical Identification

- **Bacitracin sensitive** (differentiates *Str. pyogenes* from other hemolytic streptococci – **Martens' observation**)
- **Catalase -ve**
- **PYR test Positive**.
- **NOT** soluble in 10% bile.

Culture Characteristics

- **Gram + cocci, in chains**; chain formation more pronounced in **broth media**; **longest chain** is by *Str. mitis* (**non-pathogenic**).
- **Beta hemolysis** on **blood agar**.
- **Virulent** strains produce finely granular (**matt**) colonies.
- **Avirulent** strains produce **glossy** colonies.
- **Capsulated** strains produce **mucoid colonies** corresponding in virulence to the matt type.
- Transport medium for *Streptococcus* is **Pike's medium**.

Virulence Factors

- **M protein:**
 - ▶ It is a **cell wall protein**, a **major virulence factor**.
 - ▶ It **inhibits phagocytosis**.

Capsule:

- ▶ Expressed by mucoid strains; made up of **hyaluronic acid**.
- ▶ It is **antiphagocytic**, helps in adhesion but is **NOT** antigenic in nature.

Streptococcal pyrogenic exotoxins (SPE)

- ▶ Aka **Erythrogenic/Dick/Scarlatiform** toxin.
- ▶ Three types are A, B, C; types A and C are coded by bacteriophage genes while **type B gene** is **chromosomal**.
- ▶ It is responsible for **Streptococcal Toxic Shock Syndrome** (by SPE-A); **Scarlet fever** and **necrotizing fasciitis** (by SPE-B).
- ▶ SPE (in the past) was used to identify children susceptible to scarlet fever by intradermal injection (**Dick test**) and for diagnosing scarlet fever (by **Schultz-Charlton** reaction).

DNase (Streptodornase)

- ▶ **Diagnostic use:** **Anti-DNase B** > 300-350 U is useful for retrospective diagnosis of skin infections (pyoderma) and acute glomerulonephritis where ASO titer is low.
- ▶ It helps to **liquefy thick pus/exudates** in emphysema cases.

Streptokinase:

- ▶ **Fibrinolytic** (activates plasminogen)
- ▶ Therapeutically used in treatment of coronary heart disease.

Streptolysin—see the following table.

Streptolysin O	Streptolysin S
<ul style="list-style-type: none"> • Oxygen labile (i.e. destroyed by oxygen-hence active in reduced state only) • Also heat labile • Cytotoxic for neutrophils, platelets and cardiac tissue • Strongly antigenic, hence anti-streptolysin O (ASO) titers are a standard marker for retrospective diagnosis of streptococcal infections 	<ul style="list-style-type: none"> • Oxygen stable • Serum Soluble • Responsible for hemolysis on blood agar plates • Has leucocidal activity • Not antigenic • Not useful for serological diagnosis

EXTRA EDGE

- Streptolysin O is structurally and functionally similar to:
 - Tetanolysin of *C. tetani*
 - Pneumolysin of *S. pneumoniae*
 - Theta toxin of *C. perfringens*
 - Listeriolysin O of *Listeria*
 - Cereolysin of *B. cereus*.

Anti-streptolysin-O (ASO)

- ASO is standard marker for retrospective diagnosis of streptococcal infections; included in minor criteria of Jones criteria for acute rheumatic fever.
- An ASO titer > 166 Todd units (or >200 IU) is considered a positive test.
- Test is positive in only 80% of *Str. pyogenes* (GAS) infections; **sensitivity is 80%**.
- ASO is also elevated in 20% of healthy elementary school age children (**20% false positive**)
- The sensitivity of an elevated ASO titer + anti-DNase B + antihyaluronidase (**all 3 antibodies**) is **90%**.
- ASO titers are **NOT elevated** in *pyoderma* and *post streptococcal glomerulonephritis*.

Antigenic Similarity

Streptococcal antigen	Human antigen
Cell wall M protein	Myocardium
Capsular hyaluronic acid	Synovial fluid
Group A carbohydrate	Cardiac valves
Cytoplasmic membrane	Glomerular vascular intima
Peptidoglycan	Skin antigen

Diseases Due to Strep. Pyogenes

- Pyogenic:**
 - Pharyngitis** (*S. pyogenes* is MC cause of sore throat/pharyngitis).
 - Also *S. pyogenes* is MC cause of **acute tonsillitis**; **peritonsillar abscess** (quinsy)
 - Impetigo contagiosa** (honey color crusts)
 - Erysipelas**
 - Cellulitis**.
- Toxicogenic:**
 - Scarlet fever** (sandpaper skin, strawberry tongue, Pastia's lines).
 - Necrotizing fasciitis** (by SPE-B; Aka streptococcal hemolytic gangrene; *S. pyogenes* is the MC cause; it is rapidly spreading and hence *S. pyogenes* is called 'flesh eating bug')
 - Toxic shock syndrome** (by SPE-A, a/w hypotension, multiorgan failure).
- Immunologic (non-suppurative)**
 - Rheumatic fever** ('PHaryngitis → rheumatic PHever!')
 - Acute glomerulonephritis** (MC follows skin infections)
 - Guttate psoriasis**
 - PSRA** (post-streptococcal reactive arthritis)
 - PANDAS** (Pediatric Autoimmune Neuropsychiatric Disorders A/w Streptococcal infection).

Treatment

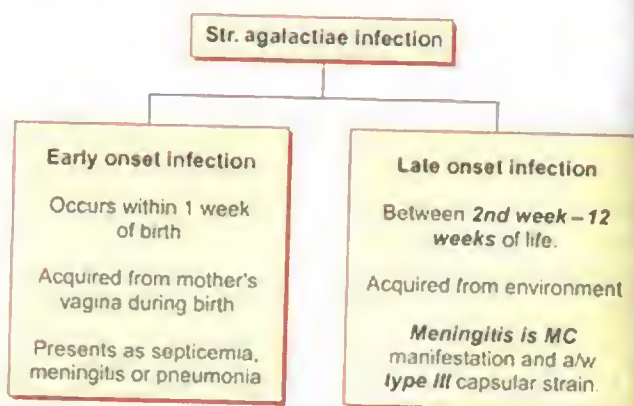
- DOC** for Strep pyogenes: **Penicillin**.
- For penicillin allergic patients-erythromycin is **DOC**.

Centor criteria

- Centor criteria for the diagnosis of **streptococcal pharyngitis** are:
 - Temperature > 38 °C
 - Tender** anterior cervical **adenopathy**
 - Absence of cough
 - Pharyngo-tonsillar **exudate** present

GROUP B STREPTOCOCCI (STREPTOCOCCUS AGALACTIAE)

- MC group B Streptococcus is *Streptococcus agalactiae*.
- Gram +ve** cocci in chains
- Bacitracin resistant**
- Hydrolyses hippurate**
- Identified by **positive CAMP reaction** (Christine, Atkins, Munch, Peterson) due to **CAMP factor** (a phospholipase).
- Colonises **female genitourinary tract**—hence infections are common in pregnancy and neonates MC cause of **neonatal meningitis** and **neonatal bacteremia/sepsis**.
- Also causes puerperal sepsis and peripartum fever.
- DOC: penicillin**.



GROUP C STREPTOCOCCI

- Human pathogen is *S. equisimilis*
- They are a part of normal flora of **throat**.
- Ferments** trehalose AND ribose (*Str. pyogenes* ferments trehalose only)

- S. equisimilis* is the source of the **drug streptokinase** used for **thrombolytic** therapy.
- Penicillin G** is the **DOC**.

VRIDANS GROUP STREPTOCOCCI

- Viridans streptococci** that are part of the normal flora of the mouth include:
 - Streptococcus sanguis* (SABE, Subacute Bacterial Endocarditis)
 - Streptococcus mutans* (causes **dental caries**)
 - Streptococcus salivarius*
 - Streptococcus mitis*
- Viridans streptococcal bacteremia** occurs in **neutropenic** patients, particularly after **bone marrow transplantation**.
- Treatment:**
 - Penicillin** is the **DOC**
 - For bacteremia in neutropenic patients, **Vancomycin** is the **DOC**.

NONENTEROCOCCAL GROUP D STREPTOCOCCI

- Includes *Strep. bovis* and *Strep. equinus*.
- Strep. bovis* **endocarditis is a/w Ca colon**.
- Can grow in bile and hydrolyse esculin BUT** cannot grow in 6.5% NaCl and **PYR negative**.
- DOC is penicillin** (susceptible).
- Aka per Harrison's 19th-*Streptococcus gallolyticus* group (formerly known as *S. bovis*), includes *Str. gallolyticus*, *Str. pasteurianus* and *Str. infantarius*.

ENTEROCOCCUS

- Enterococcus** is **NOW** a separate genus (was earlier classified under group D streptococci).
- Majority of human cases are caused by two species, *E. faecalis* and *E. faecium*. Less frequently isolated species include *E. gallinarum*, *E. durans*, *E. hirae*, and *E. avium*.
- Enterococci are **gram +ve oval cocci** arranged in pairs **spectacle eyed** appearance.
- They are normal inhabitants of the **large bowel** of human adults, although they usually make up <1% of the culturable intestinal microflora.
- Like all other streptococci** they are **catalase negative**.

Unique feature of enterococci

- Enterococci have **ability to grow** in following adverse conditions!
 - In presence of 6.5% NaCl
 - In 40% bile
 - At pH 9.6
 - At 45 °C (survives heating at 60 °C for 30 minutes)
 - In 0.1% methylene blue.

- PYR** (pyrrolidonyl-β-naphthylamide) test **positive** and **bile esculin positive**; but do NOT hydrolyse hippurate.
- Usually **non-hemolytic** (**gamma** hemolytic).
- Clinical infections:
 - Enterococci are the **second MC** organisms (after staphylococci) isolated from hospital-associated infections
 - UTI (MC infection of enterococci)** and prostatitis
 - Bacteremia without endocarditis
 - Meningitis
 - Intra-abdominal, pelvic and soft tissue infections
- Treatment:**
 - Enterococci are **intrinsically resistant** to penicillin or ampicillin alone (*E. faecium* is **most resistant**).
 - Hence **DOC is penicillin + aminoglycoside**.
 - In penicillin allergic patients: **vancomycin + aminoglycoside**
 - For **uncomplicated UTI**: Fosfomycin, ampicillin or nitrofurantoin maybe used.
 - For **ampicillin and vancomycin resistant enterococci** (mediated by *Van* gene): **Linezolid/daptomycin + aminoglycoside** maybe used.

STREPTOCOCCUS PNEUMONIAE (PNEUMOCOCCUS)

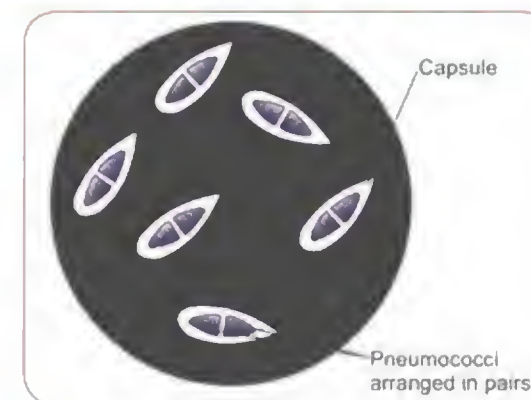


Fig. 5.11: India ink preparation showing capsule of pneumococci

Biochemical Identification

- Gram + cocci**;
- Optochin sensitive** (differentiates from *S. viridans*)
- Ferments inulin** (differentiates from other streptococci). Bile soluble.
- Grow best in 5% CO₂.

Culture characteristics

- Flame-shaped or lanceolate diplococci**
- Alpha hemolytic on blood agar-'**Draughtsman**' or '**carrom-coin**' colonies

- **Capsule** demonstrated with *India ink*
- **Quellung reaction** (Neufeld's capsule swelling reaction) seen.

Virulence Factors

- **Polysaccharide capsule:**
 - It inhibits phagocytosis.
 - It forms basis of **antigenic serotyping** and anti-pneumococcal vaccine.
 - It diffuses into culture media, tissues and exudates—hence called **specific soluble substance**
 - **Type 3 pneumococcus** has abundant capsular material; so **more virulent**.
- **IgA protease:** Degrades IgA in mucosal secretions.
- **Pneumolysin** (hemolysin):
 - Acts as a membrane damaging cytotoxin
 - Activates the complement system, causes a release of TNF- α and IL-1
 - Inhibits neutrophil chemotaxis.
- **Autolysin:** An **amidase enzyme** that cleaves peptidoglycan leading to autolysis of cells; it is responsible for **bile solubility** and **draughtsman appearance of colonies**.
- **Cell surface proteins:** Surface protein A, surface adhesin A.
- **Enzymes:** Neuraminidase and hyaluronidase.

Pneumococcal diseases

- Approximately **50%** of the normal population will have **pneumococcal colonization** in the **nasopharynx**
- **MC cause of:**
 - Community acquired **pneumonia**
 - **Meningitis** in adults (head trauma with CSF leaks, sinusitis, and pneumonia may precede it)
 - **Acute otitis media** and **sinusitis**
- **Empyema** is the MC complication of **pneumococcal pneumonia**
- **Austrian/Osler triad:** **Pneumococcal endocarditis** (usually involves the **aortic valve**) + **meningitis** + **pneumonia**.

Treatment

- **Penicillin** is the **DOC** (other beta-lactams like cephalosporins maybe used).
- Penicillin resistance is due to **altered PBP** (penicillin binding protein).
- **DOC for meningitis** is **vancomycin + ceftriaxone**.
- **DOC for ASOM** is **amoxicillin**.

Clinical Risk Groups for Pneumococcal Infection

Condition	Example
Splenic dysfunction	Post-splenectomy (asplenia), sickle cell disease, celiac disease

Contd...

Contd...

Condition	Example
Chronic respiratory disease	Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, Interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g. cerebral palsy), severe asthma
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic renal failure, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Diabetes mellitus	Diabetes mellitus requiring insulin or oral hypoglycemic drugs
Immuno-compromised	HIV infection, common variable immune deficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic corticosteroid treatment for >1 month at a dose equivalent to ≥ 20 mg/d (children, ≥ 1 mg/kg per day)
Cochlear implants	
Cerebrospinal fluid leaks	
Miscellaneous	Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters

Prophylaxis

Capsular Polysaccharide Vaccine

- It is **23-valent** pneumococcal polysaccharide vaccine (PPSV23), containing **25 μ g** of each **capsular polysaccharide**.
- Gives **80–90%** protection for about **5 years**.
- **NOT** recommended in children **< 2 years** of age.

Polysaccharide-Protein Conjugate Vaccine (PCV)

- Pneumococcal capsular polysaccharide is conjugated (coupled) to a **carrier protein** (**diphtheria toxoid**)
- Three PCV products—containing **7, 10 and 13 serotypes**, respectively—are currently (as of 2014) commercially available.
- CAN be given to **children < 2 years** old (but more than 6 weeks old).

Differences between Pneumococcus and Viridans

	Str. pneumoniae	Str. viridans
Morphology	Capsulated, lanceolate, flamed shaped	Round/oval
Arrangement	In pairs	In long chains
on blood agar	Draughtsman or carrom coin colony	Dome shaped (convex) colony
Liquid medium	Uniform turbidity	Granular turbidity
Bile solubility	Positive (soluble in bile)	Negative
Acid fermentation	Fermenter	Non-fermenter
Optochin sensitivity	Sensitive	Resistant
In vivo pathogenicity	Fatal infection	Non-pathogenic

NEISSERIA

- The genus *Neisseria* consists of **Gram negative, aerobic, non sporulating, non-motile, oxidase positive cocci** typically arranged in pairs (**diplococci**).
- The important pathogens and their differences are given as follows.

<i>Neisseria meningitidis</i> (Meningococci)	<i>Neisseria gonorrhoeae</i> (Gonococci)
Capsulated	Noncapsulated
Lens (half moon) shaped	Kidney shaped
Strict aerobes	Can grow anaerobically
Ferments both Maltose and Glucose (MeninGococci)	Ferments only Glucose, NOT maltose (Gonococci)
Rarely have plasmids	Frequently possess plasmids coding for drug resistance genes
Colony circular	Colony-vary in size with irregular margin
Habitat-nasopharynx	Habitat-Genital tract
Exist in both Intra and extracellular form	Predominantly intracellular form
Vaccine present	No vaccine

NEISSERIA MENINGITIDIS

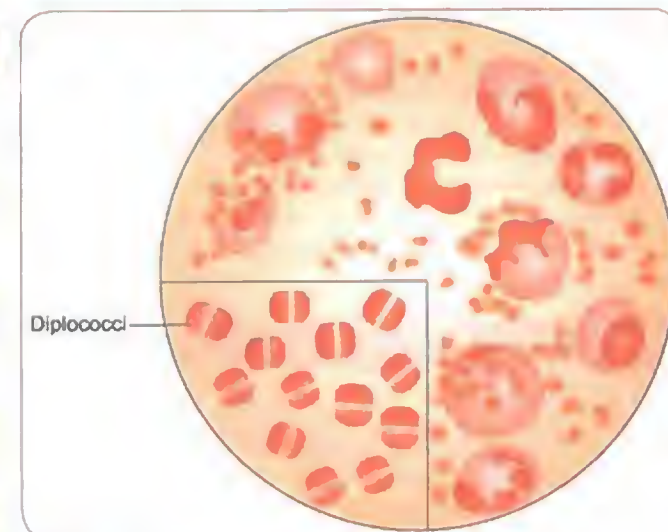


Fig. 5.12: *N. meningitidis* in cerebrospinal fluid. Inset—enlarged view showing flat adjacent side of cocci

Biochemical Identification

- **Gram -ve diplococcus** inside neutrophils
- Catalase and **oxidase positive**
- Ferments both **Maltose** and **glucose**.

Culture characteristics

- Blood agar, chocolate agar and Mueller-Hinton medium are commonly used for culturing meningococci.
- **Modified Thayer Martin** medium (with vancomycin, colistin and nystatin) is a useful selective medium.
- **Stuart medium** is **transport medium** for meningococci.

Virulence Factors

- **Capsular polysaccharide:**
 - Major virulence factor; prevents phagocytosis.
 - Based on capsular polysaccharide, 13 serogroups are identified (A–D, X–Z, 29E, W, H–I, and L), but just 6 serogroups—**A** (causes **epidemics**), **B** (**hyperendemic disease**), **C** (**outbreaks in camps**), **X**, **Y**, and **W** (formerly W135)—account for the majority of cases.
 - MC serogroup in *India* is 'A'.

- **Outer membrane proteins:**
 - *Pili*-helps in adhesion
 - *Porins* (por A and por B).
 - *Opc*
 - *IgA* protease
 - Systems for acquisition of iron-carrying proteins like *transferrin* and *lactoferrin*.
- **Lipo-oligosaccharide (LOS) endotoxin:**
 - Responsible for *fulminant meningococemia* (*purpura fulminans* or *Waterhouse Friderichsen syndrome*).

Pathogenesis

- Transmitted via *respiratory droplets*, colonize nasopharynx.
- **Carriers** are the most important source of infection.
- From nasopharynx meningococci reach meninges MC by **hematogenous** route.
- Case fatality rate is **80%**.
- Cases rapidly lose their infectiousness **within 24 hours** of specific treatment.
- Most important predisposing factor for *Neisseria* infections is complement deficiency:
 - **Defects in late/terminal complement pathway (C6-C9)** predispose to both **meningococcal** and **gonococcal** infections.
 - **Deficiency of alternate complement pathway (properdin, C3 and factor D)** predispose to **meningococcal** infection only.
 - **Hypogammaglobulinemia** and **hyposplenism**.

Diseases

1. **Meningitis:** Affects age group of 3 months to 5 years; in CSF meningococci are seen *inside neutrophils*
2. **Waterhouse-Friderichsen syndrome:** Aka fulminant meningococemia or purpura fulminans; **DIC**, **rash** and **adrenal gland failure** due to **adrenal infarction** **DOC: penicillin**.
3. Rashes, chronic meningococemia.

Diagnosis

- **Best specimen for cases:** **CSF** and **blood**
- **Best specimen for carriers:** **Throat swab**
- **Most sensitive** method for diagnosis is **PCR** amplification of DNA in CSF.
- **MC** used method is isolation of bacteria by **culture**.

Treatment

- **DOC—Third generation cephalosporin-ceftriaxone** or **cefotaxime**.
- **Prophylaxis** of contacts: Rifampicin WAS the DOC. But Harrison's 19th/1003 says it is NOT the optimal

agent and recommends **Ceftriaxone** as a *single IM or IV injection* is **highly (97%) effective** in carrying eradication and *can be used at all ages and in pregnancy*

Vaccines

- **Polysaccharide vaccine:**
 - Available against strains **A and C, Y, W135** (**MC vaccine against B**).
 - The vaccine is ineffective in children < 2 years **contraindicated** below 2 years of age and in pregnancy
 - Cold chain temperature is **+2-+8 °C**.
- **Meningococcal conjugate vaccine (MCV4):**
 - **Chemical conjugation of the polysaccharides** to a **carrier protein** (CRM197, tetanus toxoid, or diphtheria toxoid).

NEISSERIA GONORRHOEAE

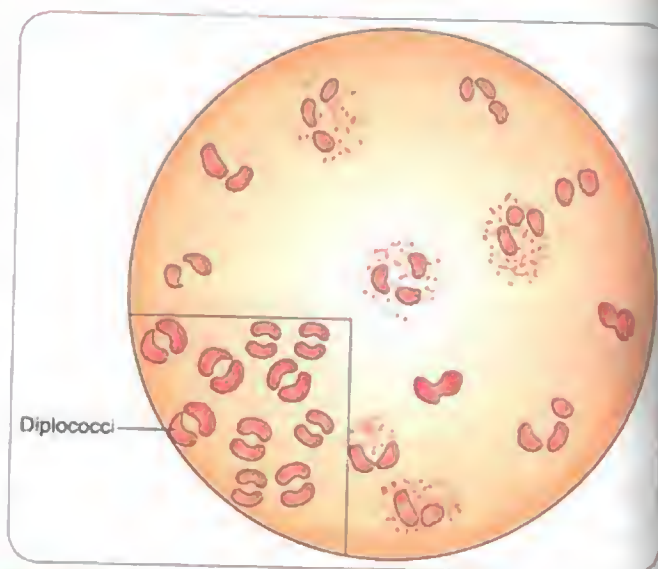


Fig. 5.13: *N gonorrhoeae* in urethral pus. Inset— enlarged view showing diplococci with adjacent surfaces concave

Biochemical Identification

- **Gram-negative, diplococci, kidney shaped** inside neutrophils.
- **Catalase and Oxidase positive**.
- **Ferments only glucose** but NOT maltose.

Culture Characteristics

- **Selective medium—Thayer martin medium**—grows as **translucent shiny colonies** (chocolate agar with antibiotics to suppress genitourinary colonizers).

Virulence Factors

- **Pili** major virulence factor for gonococci; based on pili, four types (T1-T4).
- Others: **IgA protease**; **Opacity associated protein** (protein II); **Porin** (protein I); **lipooligosaccharide** (endotoxin).

Diseases

- **Sexually transmitted disease.**
- In males:
 - **Acute urethritis** is **MC**
 - A/w **purulent urethral discharge** ('gonorrhea' is derived from 'flow of seed' resembling semen)
 - Prostate, epididymis and seminal vesicle maybe involved; **testis is spared**
 - **Chronic urethritis** ('clap') with **stricture formation** **MC in bulbar urethra**.
 - Infection may spread to periurethral tissues causing abscesses with sinus formation '**watercan**' **perineum**.
- In females:
 - The major site of primary infection in women is the **endocervix-cervicitis** is **MC**.
 - Infection may spread to cause **salpingitis, urethritis, endometritis and PID**.
 - **Vulvovaginitis** (occurs only in prepubertal children since adult vagina resistant to infection due to acid pH of vaginal secretions)
 - **Fitz Hugh Curtis** syndrome: perihepatic inflammation due to **transperitoneal spread of gonococci**.
- In both sexes:
 - Proctitis; pharyngitis (from **orogenital sex**), conjunctivitis, **ophthalmia neonatorum**; septic arthritis.

Diagnosis

- **NAAT** (Nucleic Acid Amplification Test) are sensitive and specific for gonococcal urethritis.
- **Gold standard** is isolation of gonococcus in **culture**.
- Urethral discharge is the most important specimen.
- In females best site to obtain swab is the **endocervix**.
- Transport media:
 - If processing occurs **within 6 hours:** **Stuart** or **Amies** medium.
 - If processing occurs > 6 hours: **JEMBEC** or **GonoPak** medium.

Treatment

- **DOC:** Single IM dose of **ceftriaxone**.
- For penicillin allergic patients, quinolones maybe used.

- **Spectinomycin** is an alternative also.
- Penicillin is ineffective now since **penicillinase** producing *Neisseria gonorrhoeae* (PPNG) have spread widely.

HAEMOPHILUS INFLUENZAE

Biochemical Identification

- The first free-living organism whose *entire genome* has been sequenced.
- Gram-negative; capsulated, **variable shape** (**pleomorphic coccobacilli**).
- Out of 8 biotypes, **biotype 1** is responsible for **meningitis**.

Culture Characteristics

- Cultured on **chocolate agar**, **Fildes agar** and **Levinthal medium**.
- Requires **factor V (NAD)** and **X (hematin)** for growth.
- Does not grow on blood agar.
- Shows '**satellitism**' on blood agar.

Pathogenicity

- Major virulence factor is **Type b polysaccharide capsule** (composed of polyribosylribitol phosphate).
- **Spread by aerosol/droplets**.

Feature	Type B strains	Nontypable strains
Capsule	Ribosyl ribitol phosphate	No capsule
Pathogenesis	Invasive infections due to hematogenous spread	Mucosal infections due to contiguous spread
Clinically	Meningitis , acute epiglottitis (MC cause), pneumonia and cellulitis in incompletely immunized children	Otitis media in children; In adults— exacerbation of COPD , puerperal sepsis , sinusitis
Vaccine	Highly effective conjugate vaccine	NO vaccine available

HaEMOPhilus influenzae causes

- **Acute Epiglottitis** (HiB was the MC cause, BUT now Strep. pneumoniae has overtaken due to widespread HiB vaccination)
- **Meningitis** in children < 2 years of age
- **Otitis media**
- **Pneumonia** (community acquired)—nontypable *H influenzae* is the 2nd MC cause; common among patients with **COPD** or **AIDS**

- Treat meningitis with **ceftriaxone** (since **ampicillin resistance** due to **beta lactamase** production is common); rifampicin prophylaxis in close contacts.
- Chemoprophylaxis for household contacts is **rifampicin**.
- Vaccine contains **type B capsular polysaccharide** conjugated to diphtheria toxoid or other protein. Hib conjugate vaccine given between 2 and 18 months of age.

HAEMOPHILUS DUCREYI

- Gram-negative coccobacillus; growth requires **factor X (hematin)**.
- Chocolate agar enriched with IsoVitaleX and fetal calf serum and containing vancomycin acts as selective media.
- Causes **chancroid**, (soft sore) an STD – **painful non-indurated multiple genital ulcers** (painful so 'U do cry = **ducreyi**') which bleed easily and tender inguinal lymphadenopathy (**bubo**).
- Single dose **azithromycin** is the DOC.

HACEK

HACEK

- **Haemophilus** species (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, and *Haemophilus paraphrophilus*)
- *Actinobacillus actinomycetemcomitans*
- *Cardiobacterium hominis*
- *Eikenella corrodens*
- *Kingella*

- **HACEK**: Lactose NON-fermenters are Gram-negative bacilli; all cause infective endocarditis
- All are **part of the normal oropharyngeal flora**, are slow growers, and prefer a **carbon dioxide-enriched** atmosphere. Because of their fastidious growth requirements, they have been a frequent cause of culture-negative endocarditis.

CORYNEBACTERIUM

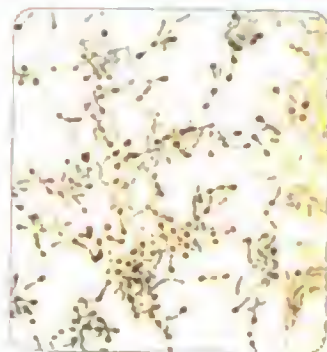


Fig. 5.14: Albert-stained smear of *Corynebacterium diphtheriae* showing metachromatic granules

Biochemical Identification

- Aka **Klebs Loeffler's bacillus**.
- **Gram +ve** bacillus, thin, **club shaped**, arranged in palisades, V or L shaped formations, **cuneiform (Chinese letter) pattern**.
- **NON capsulated** and **NON motile**.
- **Metachromatic granules** composed of polymetaphosphate (**volutin**, **Babes-Ernst**, **polar granules**) are stained by special stains-**Albert's**, **Neisser's**, **Ponder's** stains.
- **Metachromatic granules** are seen in:
 - *C diphtheriae*
 - *Gardnerella vaginalis*
 - Few *Mycobacteria*
 - *Spirillum*
 - *Agrobacterium tumefaciens*
 - *Enterobacter aerogenes*.

Culture Characteristics

- Rapid diagnosis by growth on **Loeffler's serum slope** (within 6-8 hours); **Respiratory droplet transmission**.
- From **black colonies** on **Tinsdale medium (potassium tellurite agar)** in 2 days.

Biotypes of C Diphtheriae

- McLeod classified *C diphtheriae* into 3 biotypes:
 - **Gravis** ('daisy head' colony; **starch fermentation +ve**).
 - **Intermedius** (**Frog's egg** colony, non-hemolytic).
 - **Mitis** (**Poached egg** colony, **hemolytic**, **endemic**).
- All three biotypes are **ultrate positive**.

Virulence Factor-Diphtheria Toxin

- Diphtheria toxin (DT) has two fragments.
- **Fragment B** (binding unit) binds to host cell receptors (such as EGFR) and helps in entry of fragment A.
- **Fragment A** (active unit) is internalized into the host cells and then causes → **ADP-ribosylation** of elongation factor 2 (**EF2**) → inhibition of EF2 → **irreversible inhibition of translation step of protein synthesis** → cell death.
- MOA is **similar to exotoxin A of pseudomonas**.
- The standard strain used for toxin production is the **Park Williams 8'** strain.
- DT is **heat labile**.
- All strains of **Gravis**; 95-99% strains of **intermedius** and 80-85% strains of **mitis** are toxigenic.

Factors Affecting Diphtheria Toxin

- DT is coded by **beta-prophage (corynephage)** carrying **tox+** gene.
- Toxin production depends on **optimum iron concentration** (0.1 mg/L); higher concentrations inhibit toxin formation.
- DT repressor (**DtxR**) gene is an iron dependent negative regulator of DT production and iron uptake.

Pathogenesis

- Diphtheria is a **toxemia**, but never a bacteremia.
- The **bacilli remain confined** to the site of entry, where they multiply and form the toxin—which spreads by bloodstream to various organs.
- Toxin has special affinity for **Myocardium**, **Adrenals** and **Nerve endings (MAN)**. Also kidneys and liver can be involved.

Clinical Diseases

- **Carriers** are the **MC source** of infection (than cases).
- **Nasal carriers** are **more dangerous** than throat carriers.
- Immunization **does not** prevent carrier state.
- **Partial diphtheria**:
 - **MC type** with incubation period of 2-5 days.
 - **Pseudomembranous pharyngitis**: grayish-white membrane over the tonsils may be seen.
 - Dislodging the membrane may cause bleeding.
 - Cervical lymphadenopathy may occur leading to **bull neck**.
- **Laryngeal diphtheria**: **most severe** form
- **Nasal diphtheria**: **Mildest** form
- **Cutaneous diphtheria**: may occur **without toxin formation** (non-toxigenic strain) and presents with **punched out** ulcers.
- **Complications** of diphtheria: **Myocarditis**, **polyneuropathy**, **post-diphtheritic paralysis** and **pneumonia**.
- **Trichomycosis axillaris** is dense colonization of the **axillary hair** by *Corynebacterium tenuis* which do not normally cause disease; occurs in the presence of **poor hygiene** and **hyperhidrosis**. It is a misnomer (NOT a mycosis) -but was thought to be a fungal infection).

Demonstration of Toxin

- **In vivo** tests: Subcutaneous and intracutaneous inoculation of Guinea pigs.
- **In vitro** tests:
 - Elek's gel precipitation test
 - Detection of tox gene by PCR

- Detection of DT by ELISA or immunochromatographic test (ICT).
- Cytotoxicity produced on cell lines.

Shick Test

- It was an intradermal test for finding susceptibility to diphtheria-**obsolete test** now.
- It consist of the injection of pure diphtheria toxin intradermally into a patient.
- If no inflammation occurs the patient is immune.
- If erythematous reaction occurs, person is susceptible.

Treatment

- **DOC: Penicillin** or **Erythromycin**.
- Prompt administration of diphtheria antitoxin is critical in the management of respiratory diphtheria.
- **Prophylaxis** of close contacts/carriers: 7-10 days of oral **erythromycin** or one dose of **IM benzathine penicillin G** (1.2 million units).

NON-DIPHTHERIA CORYNEBACTERIUM

- **Toxin producing**:
 - *C pseudotuberculosis* (*C ovis*)
 - *C ulcerans*
- **Non-toxigenic**:
 - *C minutissimum*: causes **erythrasma**
 - *C xerosis*
 - *C parvum* (**immunomodulator**)
 - *C urealyticum* (**UTI**, **alkaline encrusted cystitis**).

MYCOBACTERIUM TUBERCULOSIS

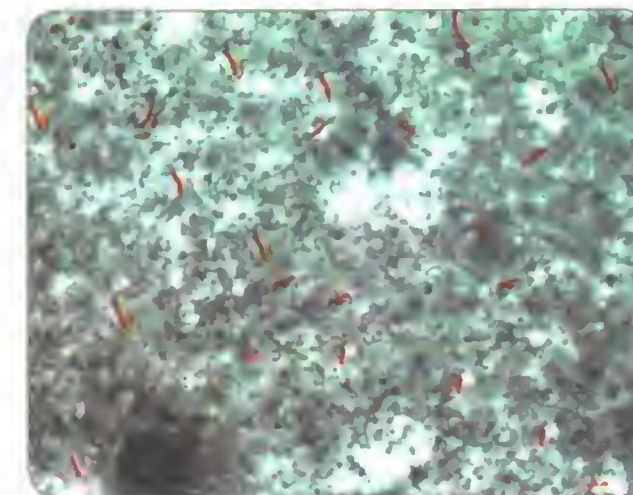


Fig. 5.15: *Mycobacterium tuberculosis* in Ziehl-Neelsen stained smear

- Discovered by Robert Koch
- Gram + rod, obligate aerobe
- **Acid fast** and stains red on **Ziehl-Neelsen stain** - due to high cell wall content of **mycolic acid**.
- Requires **Lowenstein-Jensen medium** for growth (takes 4-8 weeks for growth).
- (**Dorsett's egg, McLeod's media**) **doubling time = 18 hours** (vs 20 minutes for E coli) so can take upto 8 weeks for cultures to grow.
- Mycobacterium TB is **niacin +ve, nitrate reduction +ve** and **pyrazinamide sensitive**.
- Virulence factors: Most important is **Cord factor** (serpentine factor) allows growth in extended chains.
- For further detailed summary of tuberculosis, see respiratory system.

ATYPICAL MYCOBACTERIA (RUNYON'S CLASSIFICATION)

Classification	Infection and comments
Photochromogens	<i>M kansasii</i> <i>M simiae</i> <i>M asiaticum</i> <i>M marinum</i> (swimming pool granuloma or fish tank granuloma)
Scotochromogens	<i>M scrofulaceum</i> (scrofula, cervical adenitis in children) <i>M goodii</i> (top-water) <i>M szulgai</i> (subcutaneous bursitis)
Nonphotochromogens	<i>M avium-M intracellulare</i> complex (a/w AIDS and causes Hot tub lung) <i>M xenopi</i> (epididymitis) <i>M ulcerans</i> (Buruli ulcer) produces toxin mycolactone
Rapid growers (grow within 7 days)	<i>M chelonae</i> (Porcine heart valves) <i>M fortuitum</i>

Enterobacteriaceae mnemonics

Lactose fermenters
Citrobacter
Escherichia
Enterobacter
Klebsiella
'CHEEK'

Lactose NON-fermenters
Shigella,
Yersinia (nonmotile, no H₂S produced)
Proteus,
Salmonella (highly motile and H₂S produced)
'SHYPS'

ENTEROBACTERIACEAE

- Enterobacteriaceae are **gram-negative enteric bacilli** that are members of the family Enterobacteriaceae below:
 - *Escherichia coli*, *Enterobacter*, *Edwardsiella*
 - *Proteus*, *Providencia*
 - *Salmonella*, *Shigella*, *Serratia*
 - *Citrobacter*, *Cranobacter*
 - *Klebsiella*
 - *Morganella*
 - *Yersinia*.

ESCHERICHIA COLI

- Gram-negative rod, facultative anaerobic, motile, oxidase negative.
- Antigens are: somatic antigen **O**, capsular antigen **K** and flagellar antigen **H**.
- *E. coli* strains that cause **neonatal meningitis** possess the **K1 capsular antigen**.

Enteropathogenic E coli (EPEC)

Noninvasive, EPEC **adheres** tightly to enterocytes using intimin, leading to loss of microvilli
Has '**pathogenicity island**' in DNA
Causes **infantile diarrhea** in developing countries

Enterotoxigenic E coli (ETEC)

Noninvasive, MC cause of '**travelers' diarrhea**'
Enterotoxins: *Heat labile*, *cholera like enterotoxin* (LT) acts by stimulating cAMP. *Heat stable* toxin (ST) acts by stimulating cGMP
Sometimes causes a disease resembling *cholera* in infants (**cholera infantum**)

Enterohemorrhagic E coli (EHEC); Verotoxigenic E coli

Also called **STEC** (**Shiga toxin** or **verocytotoxin** producing E coli)
EHEC O157:H7 causes **Hemolytic Uremic syndrome (HUS)**; **hemorrhagic colitis**
Sorbitol MacConkey medio (containing sorbitol in place of lactose) is used for EHEC since it does not ferment sorbitol unlike other *E. coli*

Enteroinvasive E coli (EIEC)

Invasive (penetrate and multiply within epithelial cells); NO enterotoxins
EIEC in eyes of guinea pigs, cause keratoconjunctivitis (**Serény test**)
Invasion of **HeLa** cells in tissue culture used to identify EIEC
Produce **dysentery** clinically resembling shigellosis

Enteraggregative E coli (EAEC)

Also causes **traveler's diarrhea**, **acute and persistent diarrhea** *in vitro* they exhibit a '**stacked brick**' adherence pattern on Hep-2 cells

Enteropathogenic E coli

- UPEC utilize **P-pili** (pyelonephritis-associated pili) to bind urinary tract endothelial cells and colonize the bladder, MC cause of **urinary tract infection (UTI)** in anatomically-normal urinary tracts.
- *E. coli* with **K antigens** are MC responsible for upper UTI (pyelonephritis) while most isolates from cystitis lack K antigens.

KLEBSIELLA

- **Urease +ve**.
- *Klebsiella pneumoniae* a/w **alcoholism**, red **currant jelly sputum**; chronic bronchopulmonary disease or **diabetes mellitus**. Also causes nosocomial UTIs.
- *K. ozaenae* causes **ozena** (chronic atrophic rhinitis).
- *Klebsiella rhinoscleromatis* causes **Rhinoscleroma**.
- Carbapenems (imipenem) is **DOC**.

PROTEUS

- Gram negative, **pleomorphic**, **Urease +ve** (negative in *P. morganii*).
- **Swarming motility** with **peritrichate flagella**.
- **Swarming can be inhibited by:**
 - Increasing concentration of agar (6%)
 - Incorporation of chloral hydrate (1:500); sodium azide (1:500); alcohol (5-6%), sulfonamide, surface active agents, boric acid.
- Cultures have a '**fishy**' or '**seminal**' odor.
- **Dienes phenomenon:** Used to detect swarming growth—when two different strains of swarming *Proteus mirabilis* encounter one another on an agar plate, swarming ceases and a visible line of demarcation forms—**Dienes line** and is a/w the formation of rounded cells.
- Causes **UTI** (MC by *Proteus mirabilis*).
- A/w **struvite** (staghorn, triple phosphate) renal stones.
- Characteristic feature of *Proteus* bacilli is the **PPA reaction**.

SHIGELLA

Biochemical Identification

- Gram negative, non-motile, non-spore forming, aerobic.
- Does NOT ferment lactose except *Sh. sonnei* which is a **late lactose fermenter**.
- All ferment **mannitol** except *Sh. dysenteriae*.
- All 4 types of shigellae produce **enterotoxins**.

- Like EHEC, *Sh. dysenteriae* produces **verocytotoxin (Shiga toxin)**.
- **Infective dose** can be as low as **10-100 bacilli** since they can survive gastric acidity.

Culture Characteristics

- Transport medium is **Sach's buffered glycerol saline**.
- **Selective media** are:
 - Deoxycholate citrate agar (**DCA**)
 - **Hektoen enteric agar** (salmonella-shigella agar!)
- **Triple sugar iron (TSI)** agar is used to differentiate shigella and salmonella from other gram negative bacilli in stool culture.

Bacteria	Comments
<i>S. dysenteriae</i>	Type 1 is most virulent Causes deadly epidemics (in refugee camps, etc.) Forms exotoxins
<i>S. flexneri</i>	Antigenically most complex MC in India/developing countries Causes endemic dysentery
<i>S. boydii</i>	Resemble <i>S. flexneri</i> biochemically but not antigenically Restricted to Indian subcontinent
<i>S. sonnei</i>	It is a late lactose fermenter Mildest form of bacillary dysentery MC in developed countries

Bacillary dysentery:

- Caused by *Shigella* (*S. flexneri* in India) has a short incubation period (usually 48 hours).
- **Boiling or chlorination of water** and **pasteurization of milk** destroy the bacilli.
- Pathogenesis: (1) **invasion of the colonic epithelium** and (2) **production of enterotoxin**, which is not essential for colitis but enhances virulence.
- Abdominal pain, diarrhea, fever, vomiting and **blood or mucus in the stool**.

Complications of Shigella infection

- **Hemolytic uremic syndrome** may occur with *S. dysenteriae* infection (**Shiga toxin** also called the **verocytotoxin**)
- Toxic megacolon
- Reactive arthritis (**Reiter's syndrome**) and in children intussusception

- Detection of **virulence marker antigen (VMA)** by **ELISA** is done to detect virulence in *Shigella* and *EIEC*.
- The '**gold standard**' for the diagnosis of *Shigella* infection remains the **isolation and culture** of the pathogen from fecal material.
- Treatment: **DOC: Ciprofloxacin**.

SALMONELLA**Biochemical Identification**

- Gram-negative rod; non-capsulated and non-sporing.
- Motile by **peritrichate flagella** (except *S. gallinarum-pullorum*).
- S. typhi* and *S. paratyphi A and B* are **exclusive to humans**—no other host exists—cause typhoid fever.
- S. typhi* needs **tryptophan** as a growth factor.
- S. typhi* produces **H₂S** but *S. paratyphi* does not.
- Kauffmann-White scheme** forms the basis of serotyping of salmonellae.

Culture Characteristics

- Selenite F** and **tetrathionate broth** are used as **enrichment media** for salmonella.
- Wilson Blair sulplate** medium is **highly selective** for *S. typhi*—produces **jet black colonies** with metallic sheen (due to H₂S production).

Antigens

- Flagellar antigen H**
 - It is **strongly immunogenic** and induces antibody formation rapidly and in **high titer** following **infection or immunization**.
 - It is **heat labile** protein present on **flagella**.
 - Craigie's tube** is used to obtain cells rich in H antigen
 - H antigen **persist for longer time** than O antigens.
- Somatic O antigen (Boivin antigen)**
 - It forms an **integral part of the cell wall**.
 - It is identical to **endotoxin**.
 - It also forms **basis for classifying salmonellae** into groups.
- Flagellar Vi antigen**
 - It is **poorly immunogenic**, analogous to the K antigen of coliforms.
 - Total absence of Vi antibody in a proven case of typhoid fever indicates **poor prognosis**.
 - The antibody disappears early in convalescence.
 - Its persistence indicates the development of a **carrier state**.
 - Detection of **Vi antibody** is used as **screening test for carriers**.
 - Vi antigen used for **epidemiological typing of S. typhi**.
- H → O variation**
 - H → O variation** is a/w loss of flagella.
- Transmission is via '**Food, Fingers, Feces and Flies**'.

Enteric (Typhoid) fever

- Caused by *S. typhi* and *S. paratyphi A and B*
- Persistent **Step ladder** fever
- Diarrhea (**pea-soup** diarrhea in 3rd week)
- Headache
- Rose spots**—rash on abdomen
- Abdominal pain
- Relative **bradycardia**
- HepatoSplenomegaly
- Ulceration of Peyer's patches resulting in ulcers along the **long axis** of the bowel (**no strictures**)—occurs in 3rd and 4th week
- Salmonella osteomyelitis in long bones in **sickle cell disease**
- Can disseminate hematogenously
- Can remain in **gallbladder chronically**
- The carrier state is more common in females; male carriers are more dangerous—because of outdoor activities
- Best diagnosed by **blood culture**
- Widal test**: A test for measurement of H and O agglutinins for typhoid and paratyphoid bacilli in the patients serum
- DOC-**ciprofloxacin**
- For MDR salmonellae—ceftriaxone or azithromycin is used.

Anti-Typhoid Vaccines

- Typhoral**:
 - Ty21a**, oral live attenuated *S. typhi* vaccine.
 - Given on **days 1, 3, 5 and 7**, with a booster every **5 years**.
 - For people living in **endemic areas** the same series should be repeated every **3 years**.
 - It contains **109 viable organisms** of live attenuated Ty21A strain which lacks enzyme UDP-galactose-4-epimerase (Gal E mutant).
- Typhim Vi vaccine**:
 - Vi CPS**, a **parenteral** vaccine consisting of purified Vi polysaccharide from the bacterial capsule of Ty2 strain.
 - Given in a **single dose, SC or IM** with a booster every **2 years**.
 - Vaccine can be coadministered with other live vaccines; no serious side effect and no major contraindications.

NON-TYPHOIDAL SALMONELLAE

- Non-typhoidal salmonellae can be acquired from **animal reservoirs**.
- Transmission is with animal products (eggs, **poultry**, **undercooked meat**) and **dairy products**.
- Acute **Gastroenteritis** is **MC** due to *S. typhimurium*.

- DT-104** is a strain of *S. typhimurium* which emerged in early 1990s.
- Septicemia** maybe caused by *S. choleraesuis* (aka *S. enterica*).
- S. typhimurium* has **pathogenicity island**.

CLOSTRIDIUM

- Gram positive rods, **obligate anaerobes**, **spore forming**, highly **pleomorphic**.
- Clostridia are **motile (stately motility)** with **peritrichate flagella** except *Cl. perfringens* and *Cl. tetani* type VI.
- Capsulated clostridia** are *Cl. perfringens* and *Cl. botulinum* ONLY.
- Spores may be:
 - Spherical and terminal** (= 'drumstick') in *Cl. tetani*, *Cl. tetanomorphum*, *Cl. sphenoides*.
 - Oval and terminal** (= 'tennis racket') in *Cl. difficile*, *Cl. tertium*, *Cl. cochlearium*.
- In humans, clostridia normally reside in the **GIT** and in the **female genital tract**.
- C. perfringens* is the **MC** of the clostridial species isolated from **tissue infections and bacteremias**.

Classification**Both proteolytic and saccharolytic**

Proteolytic Predominating	Saccharolytic Predominating
<i>Cl. histolyticum</i>	<i>Cl. welchii</i>
<i>Cl. botulinum</i> A, B, F	<i>Cl. septicum</i>
<i>Cl. histolyticum</i>	<i>Cl. chauvoei</i>
<i>Cl. sordelli</i>	<i>Cl. novyi</i>
<i>Cl. sporogenes</i>	
Slightly proteolytic but not saccharolytic <i>Cl. difficile</i> ; <i>Cl. tetani</i> .	
Neither proteolytic nor saccharolytic <i>Cl. cochlearium</i> .	

Cl. perfringens (Cl. welchii)

- Gram + rod, **brick-like (boxcar)** appearance on Gram stain.
- It is **capsulated** and **nonmotile**.
- '**Stormy**' fermentation on litmus milk due to **lactose fermentation**.
- '**Target hemolysis**' on blood agar: a narrow zone of complete hemolysis by theta toxin which is surrounded by a wider incomplete hemolysis by alpha toxin.
- '**Butterfly pattern**' on **reverse CAMP** test.
- α toxin destroys cell membranes; in the presence of Ca++ and Mg++ ions, it splits lecithin into phosphorylcholine and a diglyceride.
- α toxin is **hemolytic** and shows **hot-cold** phenomenon.
- Opacity** around *Cl. perfringens* colonies is due to α-toxin.

- α-toxin is responsible for profound toxemia of **gas gangrene**.
- α-toxin is produced most abundantly by **type A strains**.
- Nagler reaction** detects α-toxin (phospholipase or Lecithinase C).
- Besides Cl. perfringens**, other bacteria that give a positive Nagler's reaction are *Cl. histolyticum*, *Cl. sordelli* and *Cl. barati*.
- Other major toxins: **beta, epsilon, theta (perfringolysin) and iota**.
- Cultured on **Robertson's cooked meat broth**.

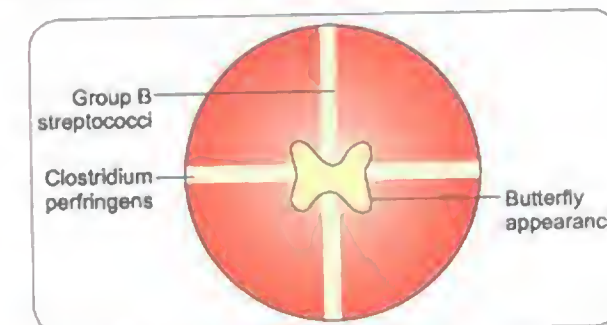


Fig. 5.16: Reverse CAMP test

Gas gangrene (clostridial myonecrosis)

- MC** caused by *Cl. perfringens* type A.
- Other clostridia causing gas gangrene are: *Cl. septicum*; *Cl. novyi*; *Cl. histolyticum*, and many other clostridia.
- Gas gangrene is caused by *Cl. perfringens* which produce **heat labile** spores.
- Infects dirty wounds, **crepitance** due to **subcutaneous gas**.
- Surgical debridement** is the **most important** prophylactic and therapeutic measure in gas gangrene.
- Citron bodies** are boat/leaf shaped pleomorphic bacilli with irregular staining in muscle biopsy diagnostic of *Cl. septicum* gas gangrene.

Clostridial Food Poisoning (Gastroenteritis)

- Caused by strains of *Cl. perfringens* which produce **heat resistant spores**.
- Due to preformed **heat labile enterotoxin**.
- Incubation period is **8–16 hours**.
- Diarrhea is prominent, but **fever and vomiting are NOT**.
- Necrotizing enteritis (pigbel)**:
 - Caused by β-toxin produced by type C strains of *C. perfringens* following ingestion of a high-protein meal in conjunction with trypsin inhibitors (e.g. in sweet potatoes) by a susceptible host who has limited intestinal proteolytic activity.

- A similar disease, *darmbrand*, was epidemic in Germany after World War II.

• Emphysematous cholecystitis:

- MC in diabetic patients.

• Treatment:

- Penicillin + clindamycin
- Surgical debridement and hyperbaric oxygen for gas gangrene.

CI Tetani

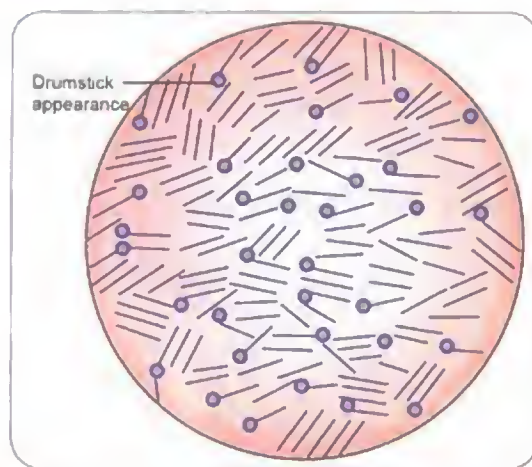


Fig. 5.17: CI tetani, some with spores and some without spores

- Gram + rod, **terminal spores** (tetani-terminal) 'drumstick' appearance.
- Toxins are a hemolysin (tetanolysin) and **neurotoxin** (tetanospasmin).
- **Tetanospasmin** is an **exotoxin** produced at site of inoculation, carried by bloodstream to peripheral nerves, transported retrograde up the axon to the proximal synapse (i.e. **acts presynaptically**, unlike strychnine, which acts postsynaptically) where it **inhibits the release of inhibitory signals like glycine and GABA**, thereby causing **unopposed stimulation of the nerve**.
- Lethal dose for a 70 kg man: **0.1 mg**.
- **Soil** acts as **source** as well as **reservoir** of infection.
- Herd immunity in tetanus: Does not protect the individual.
- **Tetanus**: Infects dirty wounds, causing permanent neuromuscular stimulation, **trismus** is the earliest feature; classically **lockjaw** from inability to relax jaw muscles, and **risus sardonicus** (sardonic smile), death is ultimately secondary to **respiratory failure**.
- **Treatment and prophylaxis**: covered under PSM chapter (Pg 465).

Clostridium Botulinum

- It is the **most potent bacterial toxin**.
- High priority (category A) **bioterrorism** agent.
- **Gram +ve** rod with subterminal spores, obligate anaerobe.
- Virulence factors: **Botulinum toxin** (it is a **zinc metalloprotease**) is preformed, **heat-labile**, absorbed in gut, carried by blood to nerve endings where it **blocks the release of acetylcholine** into the nerve synapse (i.e. it acts presynaptically).
- **Botulinum toxin type A** is being used as **therapy** for **blepharospasm, strabismus, and other dystonias**.
- Toxin of all types (A-G) are neurotoxin, except C which is a cytotoxin.
- **DOC**: antitoxin.

Types of botulism

- **Classic botulism**:
 - Symptoms begin within 12–36 hours after ingestion of food (meat products, **canned vegetables** and fish).
 - Classic '**descending paralysis**' with significant **bulbar effects** and parasympatholytic manifestations (ocular paresis, diplopia, dysarthria, dysphagia, cranial neuropathy, fixed dilated pupils, constipation, urinary retention) ultimately causing respiratory collapse in 1–7 days after onset. CNS is not affected.
- **Wound botulism**: caused by **contamination of wounds by spores** in soil, features same as classic botulism. **Type A** is most responsible.
- **Infant botulism**: **MC form** of botulism; seen after ingestion of **bacterial spores in honey**; disease usually not fatal in infants.

CI Difficile

- **Gram +ve** rod with following virulence factors:
 - **Toxin A** is an enterotoxin, and **Toxin B** is a cytotoxin, (but is 1000 times more potent in tissue cultures than toxin A).
- Diseases:
 - **Antibiotic associated colitis – pseudomembranous colitis**.
 - Seen with **antibiotic use** (2nd generation cephalosporins, clindamycin, ampicillin and fluoroquinolones).
 - Other risk factors are use of **electrical thermometers**, use of **antacids and PPI** (proton pump inhibitors) and **prolonged hospital stay**.
 - Diagnosed by the identification of **C difficile toxin in stool by tissue culture assay**.

- Biopsies reveal **epithelial ulceration with classic 'volcano' exudates of fibrin and neutrophils**.

DOC: Metronidazole* (1st line) or vancomycin (2nd choice).

- **Anti C difficile toxin B antibody** approved for prevention of pseudomembranous enterocolitis in patients on antibiotic therapy.

CI Bordelli

- **Clostridium** is a rare cause of **endometritis and toxic shock syndrome** following childbirth.
- Sudden onset **after medical abortion**; abdominal pain, absence of fever, tachycardia, severe hypotension, capillary leak syndrome with edema.
- Prolonged leukocytosis, hemoconcentration.

BACILLUS ANTHRACIS

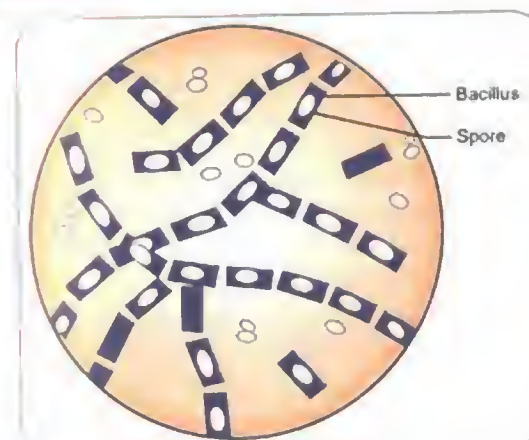


Fig. 5.18: Anthrax bacilli



Fig. 5.19: Medusa head appearance colony of anthrax bacilli

- **Gram-positive, spore forming rod**; strict **aerobe**.
- Only bacterium with a **protein (polypeptide) capsule**.
- **Anthraxoid bacilli**: **Bacillus cereus** is the most important pathogen.
- Regarding **Bacillus anthracis**:
 - **First** pathogenic bacterium observed under microscope
 - **First** communicable disease shown to be transmitted by inoculation of blood.
 - **First** bacillus to be isolated in pure culture and shown to possess spores.
 - **First** bacterium used for the preparation of an attenuated vaccine.

Types of botulism

- **Bamboostick** or **boxcar** appearance
- **Medusa head** appearance
- **Inverted fir tree** appearance
- **String of pearls** reaction
- **Frosted glass** appearance
- **Cut glass** appearance

- **B anthracis** is susceptible to gamma phage but **B cereus** is not.
- Selective medium: **PLIT** medium.
- **M'Fadyean's reaction** (to demonstrate capsule) is characteristic of **B anthracis**.
- **Duckering**-destruction of anthrax spores in animal products imported into non-endemic countries.
- **Sterne** and **Mazuchl vaccine** used to prevent anthrax in animals only.
- **Obsolete treatment** used for humans was **Sclavo's serum**.
- **Ascoli thermoprecipitation** test (identification of a cell-membrane **thermostable polysaccharide antigen**).
- Anthrax toxin is a complex of three fractions:
 - Edema factor (EF or factor I)
 - Protective factor (PF or factor II)
 - Lethal factor (LF or factor III)

Bioterrorism

- Prototypic disease: **Bacillus anthracis** (Anthrax).
- Other potential agents for **bioterrorism** are:
 - **Yersinia pestis** (**pneumonic plague**)
 - **Francisella tularensis** (**tularemia**)
 - **Variola major** (**smallpox**)
 - **Botulinum toxin** (**botulism**).

- **Pulmonary anthrax** (**Wool sorter's disease**)—following inhalation of spores flu-like symptoms that

rapidly progresses to fever, pulmonary hemorrhage, shock. X-ray shows hemorrhagic mediastinitis with mediastinal widening.

- **Cutaneous anthrax (Hide porter's disease)**—MC form of anthrax in humans; contact leads to 'charbon' / **malignant pustule (painless ulcer)** that generally resolves spontaneously. BUT 20% can progress to bacteremia and death if untreated.
- **DOC: Penicillin G.**

BORDETELLA PERTUSSIS

- **Gram-negative**, aerobic coccobacillus.
- Bipolar **metachromatic granules** seen on staining with toluidine blue.
- Strict aerobes, biologically inactive (non-fermenters).
- Aerosol transmission.
- Two members of this group are:
 - **B pertussis**: Causes **pertussis** (means 'violent cough') or whooping cough; Chinese call it '**100 day cough**'.
 - **B parapertussis**: Causes milder form of whooping cough.
- There is **no cross immunity** between *B pertussis* and *B parapertussis*.

Culture appearances of B pertussis

- Culture done on **Bordet Gengou glycerine potato blood agar** medium (diagnostic)
- Incorporation of diamidine fluoride and penicillin (**Lacey's DFP**) medium makes it more **selective**
- Appearances include '**thumb print**' appearance, '**bisected pearls or mercury drops**' or, '**aluminium paint**' appearance.

Virulence Factors

- **Pertussis toxin**: Similar to **cholera toxin** in structure and function (activated cAMP)
- Other toxins: invasive **adenylate cyclase**, **tracheal cytotoxin**, **dermonecrotic toxin**, and **lipopolysaccharide**.
- Adhesins: **filamentous hemagglutinin** (FHA); pertactin and fimbriae/pili.
- Both pertussis toxin and FHA promote secondary infection by coating *H influenzae* and pneumococci so that they can bind-known as '**piracy of adhesion**'.
- **White mouse** is often used to see experimental effects of *B pertussis*.
- '**Modulation**' is a reversible change in the capsular antigen.

Whooping Cough

- Source of infection is a case of pertussis.
- There is **NO subclinical case or chronic carrier state**.
- Period of infectivity (communicability) extends from a week after exposure to about 3 weeks after the onset of paroxysmal stage.
- More cases occur during **winter and spring months** due to overcrowding.
- It is a disease of **infants and young children (< 5 years)**. Infants are susceptible to infection from birth because maternal antibody does NOT give them protection. Incidence and **fatality are more among female** than male children.
- Mode of transmission: By **droplet infection** mainly. The role of fomites (direct contact) in the spread of infection appears to be very small, unless they are freshly contaminated.
- **Incubation period is 1-2 weeks** (7-14 days).
- The disease comprises three stages, each lasting for about 2 weeks.
 - Catarrhal
 - Paroxysmal
 - Convalescent
- **Catarrhal stage is most infective**. Secondary attack rate is high, i.e. **90%**.
- Maximum complications occur in paroxysmal stage.
- Important complications of pertussis are atelectasis, emphysema, bronchiectasis, pneumothorax, otitis media, encephalopathy, convulsions, ataxia (non-cerebellar), hernia, rectal prolapse, subconjunctival hemorrhage, intracranial hemorrhage and severe malnutrition.
- For diagnosis, **gold standard is isolation of organism in culture** from nasopharyngeal secretion.
- **Absolute lymphocytosis** occurs.
- **DOC-Erythromycin** for treatment of cases as well as for contacts.
- Isolation period is 4 week or until paroxysms cease.

Vaccines

- **Whole cell vaccine (killed)**
 - Usually administered as DPT at intervals of 4 weeks before the age of 6 months.
 - Can cause neurological complications with a risk of 1:170000.
 - Contraindicated in children > 5 years age.
- **Acellular pertussis vaccine**:
 - It contains pertussis toxoid, FHA, pertactin and fimbrial antigen.

- It is recommended for all infants, combined with diphtheria and tetanus toxoids (DTaP).
- Causes less neurological complications.

BRUCELLA

- Gram-negative coccobacillus; strict aerobe.
- Nomenclature system of classification is used for Brucella (13 species).
- **Brucella melitensis** is **most pathogenic** followed by *Br abortus* and *Br suis*.
- **B melitensis is MC** cause of brucellosis in humans; it usually infects **goats, sheep and cattle a zoonosis**.
- Grows on media containing **erythritol** (hence Brucella prefers placenta also due to the presence of erythritol in placenta) and it is **capnophilic** (requires CO₂).
- Transmission:
 - **Direct contact (MC mode)** with infected animal tissue or infected placenta.
 - **Food borne**: from **UNpasteurized milk** or milk products, raw **meat**.
- There is **NO** evidence of man-to-man transfer.
- **Brucellosis**
- Aka **Undulant fever (Malta fever or Mediterranean fever)** fever waxes and wanes daily
- **Classic triad**: fever, night sweats and hepatosplenomegaly (affects reticuloendothelial system).

Diagnosis of brucellosis

- **Blood culture** is definitive (**Castenada's method**)
- Serology (STA - standard tube agglutination with **2 ME**, mercaptoethanol - low sensitivity/specificity)-used **ONLY** for **acute Brucellosis** since it detects **IgM**.
- Tests for detection of brucellosis in cattle: **Rose Bengal card test**; **Rapid plate agglutination test**.
- Tests for detection of brucellosis **in milk**: **Milk ring test**; **whey agglutination test**.

- **DOC**: doxycycline + an aminoglycoside.
- WHO regimen: Rifampicin + doxycycline
- Prophylaxis: Pasteurize milk - pasteurization kills brucella.

MYCOPLASMA

Basic Features

- **Smallest (150-350 nm) free-living organisms** and are prokaryotes.
- Pleomorphic, filterable; replicate by **binary fission**.
- **NO cell wall**, hence NOT seen on Gram stain; better stained by **Giemsa stain or Diene's stain**.

Culture

- Mycoplasma can be cultivated in solid or liquid media (cell free media).
- **Require cholesterol** for growth.
- Colonies have a '**fried egg**' appearance.
- Cultivated on **Eaton's agar**, mycoplasma is also called '**Eaton agent**'.

Infections caused by Mycoplasma

- **Respiratory**: *M pneumoniae*
- **Genital**: *M hominis*, *Ureaplasma urealyticum*, *M genitalium*
- **Primary atypical pneumonia, 'walking' pneumonia** (minimal clinical signs but **marked** X-ray evidence of consolidation) - seen in teen/young adults, increasing nonproductive cough, self-limiting in most cases.
- Extrapulmonary infections: **Bullous myringitis**, otitis, skin rashes and hemolytic anemia.
- High titer (> 1:32) of **cold agglutinins (IgM)** suggests diagnosis of *M pneumoniae*.
- Treatment: **DOC-Macrolides** (erythromycin/azithromycin) or **tetracyclines**; **penicillin is ineffective** since no cell wall is present.
- *Mycoplasma hominis*: UTI, pyelonephritis, pelvic inflammatory disease and postpartum fevers, sternal wound infections in heart-lung transplant recipients.

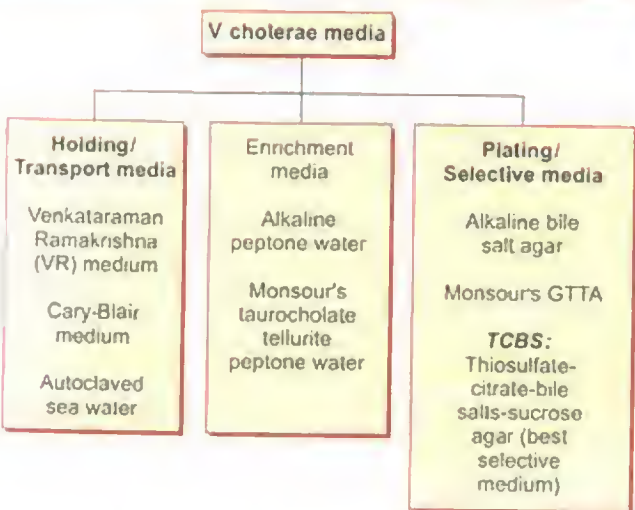
VIBRIO CHOLERA

Identification

- **Gram -ve, comma shaped rod**, strict/obligate aerobe.
- **Darting motility** (shooting star motility) by a **polar flagellum**; actively motile vibrios resemble a '**swarm of gnats**'.
- Arranged in parallel rows producing '**fish in stream**' appearance.
- '**COINSS**' = Catalase +ve; Oxidase +ve; Indole +ve; Nitrates are reduced to nitrites; Sucrose fermenter; '**String test**' +ve.
- Indole and nitrate positive = **cholera red reaction**.
- **Susceptible** to 0/129-vibriostatic agent.

Culture Characteristics

- Growth is better in **alkaline** medium; **optimum pH is 8.2**.
- Vibrios are **susceptible to heat drying** but **resist high alkalinity**.
- **NaCl (0.5-1%)** stimulates growth; however higher concentrations (> 6%, hypertonic saline) are inhibitory.
- **Not nutritionally fastidious** and grows well on ordinary media.



Gardner and Venkataraman Classification

- Cholera vibrios and biochemically similar vibrios possessing a common flagellar antigen (H) are classified as **group A** vibrios and the rest as **group B** vibrios.
- V cholerae has 'O' **lipopolysaccharide** that confers serologic specificity.
- There are at least 200 serogroups (O1-O200).
- O1 strain** WAS responsible for all 6 pandemics and most of the epidemics of cholera.
- All strains **other than O1** are called '**non-agglutinating**' (**NAG**) vibrios (since they are not agglutinable with O1 antiserum); aka **non-cholera vibrios**.
- O139 strain** is called **Bengal strain V cholerae**—was identified newly in 1992 (in Chennai) and caused outbreaks of cholera in India and Bangladesh. O139 is **capsulated**.
- Group O1 is further subdivided into '**classical**' and '**El tor**' biotypes—both have three serotypes—Ogawa, Inaba and Hikojima.
- Ogawa serotype of El tor** is the **MC strain** causing cholera (current 7th pandemic). MC biotype in India also.

Unique Features of El Tor Vibrio (Vs Classical Vibrio)

- Much tougher! **Capable of surviving** in environment for longer.
- Severity is lesser**, with large proportion of mild/asymptomatic infections.
- Mortality is low** BUT carrier state is high (**1:90 for El tor** compared to 1:50 for classical type).
- Fewer secondary cases in affected families (**secondary attack rate is less**).

	Classical	El tor
b-hemolysis on sheep blood agar	Negative	Positive
Chick erythrocyte agglutination	Negative	Positive
Polymyxin B (50 IU)	Sensitive	Resistant
Group IV phage susceptibility	Susceptible	Resistant
El tor phage V susceptibility	Resistant	Susceptible
Voges Proskauer (VP) test	Negative	Positive
CAMP test	Negative	Positive
Cholera toxin gene	CTX-1	CTX-2

Virulence Factors

Cholera toxin

- Enterotoxin composed of two subunits, A and B
- Subunit A**, has two fragments A1 and A2.
- Fragment A1, ADP-ribosylates G protein locking it in the stimulatory mode resulting in overwhelming production of cAMP → secretion of chloride ion and water in the small intestine
- Fragment A2, links A1 fragment to B subunit.
- Subunit B**, binds to **GM1 ganglioside receptors** on GI epithelium; it is necessary for penetration of subunit A into the cell.
- V cholerae** acts by **disrupting tight junctions**.
- Cholera toxin production is determined by a **filamentous phage** integrated with bacterial chromosome.

- Zona occludens toxin**: **disrupts tight junctions** between mucosal cells.
- Siderophore**: Required for iron acquisition.
- Lipopolysaccharide**, LPS (bacterial endotoxin): **unlike** other gram-negative bacilli, LPS in V cholerae does **NOT** contribute to pathogenesis of cholera, BUT it is immunogenic and is included as a component of killed vaccines.

Cholera

- Incubation period: 24–48 hours.
- Painless watery diarrhea (rice water stools)**.
- NO bloody stools, NO abdominal pain, NO fever; death is due to **dehydration and electrolyte imbalance**; **diarrhea is secretory**, originates in small intestine.
- Neutrophilia may be present.
- Treatment: ORS, **glucose must be included** in the ORS to increase ion uptake in the gut **via sodium glucose cotransporter**.
- DOC for adults is single dose **tetracycline or doxycycline**.

- Funazolidine is the DOC in pregnant women.
- Mass chemoprophylaxis is NOT indicated.
- DOC for prophylaxis is tetracycline.

Epidemiology of Cholera

- Homeland** of cholera: Cholera is native to the **Ganges delta** in the Indian subcontinent.
- Since 1817, seven global pandemics have occurred: All were caused by **classical O1 strain** which started in Bengal and spread to the world.
- Seventh pandemic** started in 1961; the **ONLY** pandemic to have **originated outside India (started in Indonesia)**; it is caused by **El tor biotype**.
- The natural habitat of V cholerae is coastal salt water and brackish estuaries where the organism lives in close relation to plankton and where it may survive in a viable but nonculturable form.
- Transmission** is by **feco-oral** route.
- Man** is the **ONLY** reservoir.
- Chlorination** of water is effective against V cholerae.
- Persistence** of V cholerae:
 - During epidemics: maintained by carriers and sub-clinical cases.
 - During interepidemic period: in sea water, crustaceans and planktons.
- Resistance** of V cholerae:
 - Stable to alkali and refrigeration (can remain in ice for 1–6 weeks!)
 - It is **heat labile** and **acid labile**.
- For assessing **prevalence of cholera**, complement dependant vibriocidal antibody test is most useful.

Cholera Vaccines

- Injectable killed vaccine**: no longer in use.
- Oral Cholera Vaccines (OCV)**: Killed whole cell vaccine; two types exist.

(WC/rBS, Dukoral)

- Made in **Stockholm, Sweden**.
- Whole cell recombinant B subunit cholera vaccine
- Two doses given at 7 days gap; CI in children < 2 years.
- Children better protected than adults.
- WHO recommends using this vaccine **during** community epidemics.

IlvWC

- Made in **Mumbai, India**.
- It contains several biotypes and serotypes of V cholerae O1 and V cholerae O139 BUT NO cholera toxin B subunit.

Oral Live Attenuated Vaccine

- Still under development.
- CVD-103 HgR was developed but NO longer in use.

HALOPHILIC VIBRIOS

- These have **absolute requirement of salt** for growth (cannot grow in absence of salt).
- Can withstand **high salty concentrations** (> 6%).
- Human infection commonly follows the **ingestion of seawater** or of **raw or undercooked shellfish**.
- Most halophilic (**noncholera vibrios**) can be cultured on blood or **MacConkey agar**, which contains enough salt to support the growth of these halophilic species.
- Gastrointestinal** illness (due to **V parahaemolyticus**, **non-O1/O139 V cholerae**, **Vibrio mimicus**, **Vibrio fluvialis**, **Vibrio hollisae**, and **Vibrio furnissii**).
- Soft tissue** infections (due to **V vulnificus**, **Vibrio alginolyticus** and **Vibrio damsela**).

Organism	Comments
V parahaemolyticus	Causes: Gastroenteritis and wound infection. Enteropathogenicity of V parahaemolyticus is linked to its ability to cause hemolysis on Wagatsuma agar (i.e. the Kanagawa phenomenon).
V vulnificus	Also called L+ vibrio since it ferments lactose . Causes: Primary sepsis (a/w underlying liver disease, iron overload-hemochromatosis and immunosuppression) and primary wound infection.
V alginolyticus	Most salt tolerant vibrio. Causes Otitis media and eye infections.

LEGIONELLA PNEUMOPHILIA

- Gram-negative rod; Gram stains poorly – use **silver stain**; Strict aerobe.
- Grows on complex media like buffered **charcoal yeast extract (BYCE)** agar with cysteine and iron.
- L. pneumophila serogroup 1** accounts for nearly all severe infections; **serogroup 6** is more commonly involved in **hospital outbreaks**.
- Transmission:
 - MC mode is aspiration via oropharyngeal colonization.
 - Aerosolization: **Aerosol transmission** from environmental water source (**air conditioners**, cooling towers, showers, sinks).
 - NO person to person transmission.
 - The source of **Legionella** is water.

Clinical features: Legionella

- **Legionnaires' disease** (severe pneumonia) first recognized in 1976, at a Philadelphia hotel during the American Legion Convention.
- **Pontiac fever** is mild flu, NO pneumonia.
- Clinical clues for Legionnaire's disease are **multilobar pneumonia, high fever, hyponatremia, diarrhea**, numerous neutrophils but NO organisms revealed on Gram staining of respiratory secretions.
- MC extrapulmonary site of infection is the **heart** (myocarditis).

Treatment

- **Aminoglycosides** plus extended-spectrum penicillin (**piperacillin, ticarcillin**)
- Cephalosporins with antipseudomonal activity
- **III generation (ceftazidime and cefoperazone)**
- **IV generation (cefpirome and cefepime)**
- **I and II generation cephalosporins** have limited or NO activity against *Pseudomonas*.

Other Pseudomonas Organisms

- ***Pseudomonas (Burkholderia) pseudomallei*:**
 - Aka **Whitmore's bacillus**.
 - Aerobic Gram negative motile bacillus.
 - Bipolar staining seen with methylene blue stain
 - Causes **melioidosis** (**Vietnamese time bomb disease**) acute pulmonary disease is MC
 - **DOC Cefotaxime**.
- ***Pseudomonas (Burkholderia) mallei*:**
 - Aerobic Gram negative NON-motile bacillus
 - Causes **glanders and farcy**
 - Mallein test is a skin test like tuberculin test
 - Strauss reaction (intraperitoneal injection in mice causes testicular swelling).

ACTINOMYCES AND NOCARDIA

Actinomyces	Nocardia
<ul style="list-style-type: none"> • Weakly Gram-positive branching filamentous bacterio, NOT acid fast, anaerobic • Causes abscesses and invasive infections – Cervicofacial (MC); Thoracic; Abdominal, dental. Readily crosses tissue planes and erodes through bones, causing sinus tracts that drain from organs through the skin • Yellow sulfur granules—may be found in the pus; granules are bacterial colonies consisting of gram positive filaments surrounded by peripheral zone of swollen club shaped structure ('sun-ray' appearance) • DOC: Penicillin G is the drug of choice 	<ul style="list-style-type: none"> • Weakly Gram-positive or do not Gram stain, Acid fast (esp. with modified Kinyoun acid-fast stain using weak acid-1% sulfuric acid); Z-N stain), aerobic, thin filaments or rods, can cause eosinophilia, found in soil • Causes pneumonia, meningitis and brain abscess, subretinal abscess, endophthalmitis, in immunocompromised, cellulitis, keratitis, actinomycetoma and disseminated disease • Histologically abscess extensively infiltrated with neutrophils • DOC: Sulfonamides (TMP-SMX)

PSEUDOMONAS**Identification**

- **Gram -ve rod, NON sporulating, motile** by single polar flagellum
- NON lactose fermenting
- Oxidase positive
- Freelifing in water and soil
- **Obligate Aerobic**.

Culture Characteristics

- Produce the **blue-green pigment pyocyanin**
- Fruity (**grape-like**) odor or '**corn taco**' like odor
- **Fluorescences** under UV light
- Grows well on most media
- **Cetrimide** agar is **selective media**
- **Cetrimide** and **Dettol** (chloroxylenol) have been incorporated in the media for selective isolation.

Virulence Factor

- **Major virulence factor: Diphtheria toxin-like exotoxin A** that inactivates causes the ADP ribosylation of eucaryotic elongation factor 2 (**EF-2**) resulting in inhibition of protein synthesis in the affected cell.

Important pseudomonas diseases

- **Skin: Ecthymo gangrenosum**, hot tub folliculitis.
- **Bacteremia**: Predisposing conditions include **severe burns and immunosuppression**.
- **Lungs: Bacteremic pneumonia**, in neutropenic cancer patients undergoing chemotherapy.
- Chronic LRTI in **cystic fibrosis**.
- **Ear: Swimmer's ear** innocuous; **Malignant otitis externa** in elderly diabetics.
- **Eye**: Bacterial keratitis (**corneo perforates** within 48 hours!), endophthalmitis.
- **GIT: Shanghai fever** (gastroenteritis).



Fig. 5.20: Sun-ray appearance of actinomycetes

LISTERIA MONOCYTOGENES

- **Gram-positive bacilli**, facultative intracellular.
- Shows **tumbling motility** at 25 °C but at 37 °C it is non-motile.
- Acquired by ingestion of **unpasteurized milk/cheese** or by vaginal transmission during birth.
- From '**actin rockets**' by which they move from cell to cell.
- Virulence factors – **Listeriolysin O**, disrupts cell membranes oxygen labile and immunogenic.
- Diseases:
 - **Granulomatosis infantisepticum** is a **neonatal** infection acquired **in utero** and characterized by disseminated abscesses, granulomas and a high mortality rate.
 - **Neonatal meningitis, Amnionitis, septicemia and spontaneous abortion** in pregnant women.
 - Meningitis in immunocompromised adults. CSF shows **neutrophilic pleocytosis**.
- **PVICAM, Oxford and LPM** are the most frequently applied plating media.
- **Chromogenic culture** media may be used.
- Anton test: obsolete test now; instilling test material into rabbit eyes caused conjunctivitis.
- DOC: **ampicillin with gentamicin**.

CAMPYLOBACTER

- **Gram -ve**, NON capsulated; NON sporing; **comma/'gull wing'** shaped, motile bacillus.

- Grows under **microaerophilic** conditions (5% O₂, 10% CO₂, 85% N₂).
- **Thermophilic**, growing at **42 °C** (can grow at 37 °C but incubation at higher temperatures suppresses normal fecal flora).
- MC *Campylobacter* disease is **diarrhea**.
- **Gullain Barre syndrome** may follow campylobacter infection.

YERSINIA PESTIS

- Gram -ve, non-motile coccobacillus.
- **Wayson** or Giemsa or methylene blue stain shows typical bipolar staining with safety pin appearance.
- **Stalactite** growth on ghee broth.
- Causes plague-aka **Black death/Mahamari**.
- Wild rodent (**Tatera indica**) is the **natural reservoir** of *Yersinia pestis* in India (zoonoses).
- MC vector is the rat flea-*Xenopsylla cheopis*.
- A partially blocked flea is more dangerous (a flea with a partially blocked proventriculus) than a completely blocked flea.
- Transmitted by **bite** of infected flea or **direct contact** with tissues of flea.
- Three types of plague are:
 - **Bubonic plague (MC type)** with incubation period **2-7 days**; a/w **fever, chills** and **enlarged tender and painful lymph nodes**.
 - **Pneumonic plague (most virulent** and least common) with incubation period **1-3 days**; affects respiratory system and highly infectious.
 - **Septicemic plague** (less infectious).
- Treatment:
 - DOC-streptomycin;
 - DOC for **prophylaxis**: Tetracycline

YERSINIOSIS

- **Yersiniosis** is a **zoonotic** infection with an enteropathogenic *Yersinia* species, usually *Yersinia enterocolitica* or *Y pseudotuberculosis*.
- *Y enterocolitica* is more closely associated with **terminal ileitis** and *Y pseudotuberculosis* with **mesenteric adenitis**, but both organisms may cause **mesenteric adenitis** and symptoms of **abdominal pain and tenderness** that result in **pseudoappendicitis**, with the surgical removal of a normal appendix.

LEPTOSPIROSIS

- **Leptospirosis** is a **zoonosis** caused by the multiple serovars of *Leptospira interrogans*.

- Transmitted to humans by the *ingestion of food/drink contaminated by the rat's urine (reservoir animal)*; occupational disease among *sewer workers, rice planters, abattoir workers, farmers*.
- Outbreaks occur after *floods*.
- Incubation period = **2–20 days**.
- Anicteric leptospirosis**: MC and milder form of the disease.
- Icteric leptospirosis (Well syndrome)**: MC caused by *L. icterohemorrhagica* impaired *kidney and liver function (jaundice)*, *abnormal mental status, petechial rash and hemorrhagic pneumonia*; has a **high (5–40%) mortality rate**.
- Diagnosis**: *Neutrophilic leukocytosis*; urine may contain bile, protein, casts and red cells; oliguria is common; *elevated bilirubin and aminotransferases*; *elevated serum creatinine*; *dark field microscopy* of the patient's blood; **Culture** on a semisolid medium (e.g. Fletcher EMJH); diagnosis is usually made by means of *serologic tests* (ELISA, PCR)
- Treatment: **Penicillin** or **ceftriaxone** is the **DOC in severe leptospirosis**; **Doxycycline** or **azithromycin** (macrolide).

CHLAMYDIAE

- They are obligate intracellular parasites.
- 2 forms exist:
 - **Extracellular elementary body** which enters cell via endocytosis
 - **Initial or reticulate body**, which replicates in cell by **binary fission** to produce daughter **elementary bodies** seen as inclusion bodies **in the cytoplasm** of cell seen by Giemsa stain.

Transmission

- C pneumonia* transmitted via *respiratory droplets*.
- C psittaci* via inhalation of *bird (pigeon) feces*.
- C trachomatis* via sexual contact or vertically at birth, and causes eye disease by direct finger/fomite to eye contact.

Inclusion Bodies

- C trachomatis* causing conjunctivitis: **Halberstaedter-Prowazek bodies**.
- C trachomatis* causing LGV: **Miyagawa's** granulocorpuscles.
- C psittaci*: **Levinthal-Cole-Lillie** bodies.

Treatment

- Erythromycin** or **doxycycline**.

Diseases caused by Chlamydiae

- *C pneumonia* – (only **1 serotype**); otitis, bronchitis, sinusitis, atypical pneumonia, **'staccato cough'**; atherosclerosis and coronary artery disease.
- *C psittaci* causes **psittacosis**, pneumonia, high fever, headache.
- *C trachomatis*:
 - Serotypes **A–C** cause **trachoma**
 - Serotypes **D–K** cause **genitourinary infections** (urethritis/PID, ectopic pregnancy)
 - Serotypes **L1–L3** cause **lymphogranuloma venereum**.

RICKETTSIAL DISEASES

	Disease	Agent	Vector
Typhus group	Epidemic typhus (Brill Zinsser disease)	<i>R. prowazekii</i>	Louse
	Endemic/Murine typhus	<i>R. typhi</i> (<i>R. mooseri</i>)	Flea
Spotted fever group	Rocky mountain spotted fever (RMSF)	<i>R. rickettsiae</i>	Tick
	Rickettsial pox	<i>R. akari</i>	Mite
	Indian tick typhus, <i>Boutonneuse</i> fever	<i>R. conorii</i>	Tick
Other	Q fever	<i>Coxiella burnetii</i>	Nil-No arthropod (airborne)
	Trench fever (five-day fever)	<i>R. quinatana</i> (<i>Bartonella quinatana</i>)	Louse
	Scrub typhus (Chigger borne typhus)	<i>R. tsutsugamushi</i>	Mite
	Ehrlichiosis	<i>Ehrlichiae</i>	Tick

Rickettsiae—Important Points

- Rickettsiae are **gram negative obligate intracellular organisms except for *R. quintana***.
- Among Rickettsial disease, **transovarian transmission** is seen in **scrub typhus**.
- Main pathogenesis of rickettsial disease is due to damage to **vascular endothelium**.
- NO rash in Q fever.
- NO eschar in epidemic typhus and RMSF.
- Neil Mosser** reaction or **tunica reaction** positive in *R. typhi*, *R. conorii*, *R. akari* and negative for *R. prowazekii*.
- Well Felix** reaction-**heterophile agglutination test** based on sharing of alkali stable polysaccharide between typhus rickettsia and some strains of *Proteus* bacilli (OX19, OX2 and OXK):

- **OX19 (+++)** in epidemic and endemic typhus
- **OX2 (++)** in rocky mountain spotted fever

- **OXK (+++)** in scrub typhus
- **No value** in Q fever, trench fever and rickettsial pox.

VIROLOGY

Classification of DNA Viruses

Capsid symmetry	Virion: Enveloped or naked	Physical type of nucleic acid	Virus family	Examples
Icosahedral	Naked	SS	Parvoviridae (smallest virus size)	Parvovirus B19 (only virus to have ssDNA)
		DS circular	Papovaviridae	Human Papilloma Virus Polyoma virus (JC virus, BK virus, Merkel cell virus)
		DS	Adenoviridae	Adenovirus
	Enveloped	DS	Herpesviridae	HSV1 and HSV2 VZV EBV CMV HHV6 and HHV7, HHV8 (a/w Kaposi's sarcoma)
		DS circular	HepaDNAviridae	Hepatitis B virus
Complex	Complex coats	DS	Poxviridae (largest virus size)	Variola Vaccinia Orf Moluscum contagiosum virus

Classification of RNA Viruses

Capsid symmetry	Virion: Enveloped or naked	Physical type of nucleic acid	Virus family	Examples
Icosahedral	Naked	SS (+)	PicoRNAviridae	Poliovirus Coxsackievirus Echovirus Enterovirus Rhinovirus Hepatitis A virus
			Caliciviridae	Norovirus Hepatitis E virus Rubella virus
			Reoviridae	Rotavirus Reovirus Colorado tick fever virus
	Enveloped	SS (+)	Togaviridae	Rubella virus Eastern equine encephalitis virus Western equine encephalitis virus
		SS (+)	Flaviviridae	Yellow fever virus Dengue virus St. Louis encephalitis virus West Nile virus Hepatitis C virus Hepatitis G virus

Contd...

Contd...

Capsid symmetry	Virion: Enveloped or naked	Physical type of nucleic acid	Virus family	Examples
Helical	Enveloped	SS	Retroviridae	Human T lymphotropic virus types 1 and 2 Human immunodeficiency virus types 1 and 2
		SS segmented	Bunyaviridae	Hantavirus California encephalitis virus Sandfly fever virus
		SS segmented	Orthomyxoviridae	Influenza A, B, and C viruses
		SS segmented	Arenaviridae	Lymphocytic choriomeningitis virus, Lassa fever virus South American hemorrhagic fever virus
		SS (+)	Coronaviridae	Coronaviruses
		SS	Paramyxoviridae	Parainfluenza virus Respiratory syncytial virus Newcastle disease virus Mumps virus Rubeola (measles) virus
		SS	Rhabdoviridae	Rabies virus Vesicular stomatitis virus
		SS	Filoviridae	Marburg virus Ebola virus

Inferences from the Above Tables are:

- **DNA viruses:**
 - **HHAPPPy** viruses: Herpes, Hepadna, Adeno, Parvo, Papilloma, Pox viruses
 - In the above, APP are **Naked DNA viruses** (Adeno, Parvo, Papilloma, viruses)
 - All are double stranded (dsDNA) **except** Parvovirus (ssDNA)
 - All replicate in the nucleus **except** Pox (carries own DNA-dependant RNA polymerase)
 - All have **icosahedral** symmetry **except** Poxvirus (complex)
- **RNA viruses**
 - All are single stranded (ssRNA) **except** Reovirus (double stranded, dsRNA)
 - **Naked RNA viruses** are Picorna, Calici and Reoviruses (PCR)
 - All replicate in cytoplasm **except** influenza and reoviruses
 - **Segmented RNA viruses** are Bunya (3 segments), Orthomyxo (8 segments), Arena (2 segments), Reoviruses (11) ('**BOAR**': 'Thre(e)igh(t)wo-eleven'; 3-8-2-11)
 - RNA viruses with **negative sense RNA**: Arenavirus; Filovirus; Rabies (Rhabdovirus); Myxovirus (ortho-

myxo and paramyxo); Bunyavirus. ('**Arre Fillow**, don't eat **Rabies Myxed Bun!!**').

GENERAL VIROLOGY

Size of Viruses

- Size of virus maybe determined by ultrafiltration, ultracentrifugation or electron microscopy.
- **Largest virus:** POX virus (320 nm)
 - **Smallest virus:** Parvovirus; 20 nm (also remember that parovirus is ssDNA; ss = 'small small !!')
 - **Smallest RNA virus:** Picornavirus
 - **Largest RNA virus:** PARAMYXOVirus.

Shapes of Viruses

Virus	Shape
Rabies virus	Bullet shaped
Tobacco mosaic virus	Rod shaped
Rotavirus	Wheel shaped
Pox virus	Brick shaped
Adenovirus	Space vehicle shaped
Astrovirus	Star shaped peplomers
Ebolavirus	Filamentous shaped
Coronavirus	Petal shaped peplomers

Cultivation of Viruses

As viruses are **obligate intracellular parasites**, they cannot be grown in cell free artificial/inanimate media. Methods employed for cultivation of viruses are:

1. **Animal inoculation:**
 - **Suckling mice:** Used for cultivating **Coxsackie** and **Arboviruses**.
 - **Coxsackie A** produces **flaccid** paralysis; **Coxsackie B** produces **spastic** paralysis.
2. **Embryonated egg inoculation:**
 - **Chorioallantoic** membrane: Visible pox are produced, e.g. vaccinia, variola, HSV1 and HSV2
 - **Amniotic** sac: Influenza, mumps
 - **Yolk sac:** **Arboviruses** (JE virus, Saint Louis virus, West Nile virus); **Rickettsiae**, **Chlamydiae**, **H. ducreyi**
 - **Allantoic** culture: Used for preparing vaccines for influenza, Yellow fever (917D) and Rabies (Flury).
3. **Tissue culture:**
 - **Organ** culture: Whole organ is used; **tracheal ring** used for **coronaviruses**
 - **Explant** culture: Minced organ is used, e.g. **adenoid** explant used for **adenovirus**.
 - **Cell lines:** Tissues are completely digested and the individual cells are mixed with vital growth media and dispensed in tissue culture flasks. **MC used method** for virus isolation.

Cell Lines

- **Primary cell lines:** Cannot be maintained in serial cultures; undergo limited divisions (5-10). Examples are:
 - Rhesus kidney cell line—used for myxoviruses, enteroviruses and adenoviruses.
 - Human amniotic cell line; chick embryo fibroblast.
- **Secondary (Diploid) cell lines:** Can be maintained in serial culture for limited number of times (10-50). Examples are:
 - **Human fibroblast** cell line used for CMV.
 - **MRC-5** and **WI-38** (human embryonic lung cell strain).
- **Continuous cell lines:** derived from **cancerous** cells; hence have **indefinite** divisions and possess haploid chromosomes. They are easy to maintain in lab by serial subculturing.
 - **HeLa** cell line: Human carcinoma of cervix cell line
 - **HEp-2** cell line: Human epithelioma of larynx cell line (used for RSV, HSV, adenovirus isolation)
 - **KB** cell line: Human carcinoma of nasopharynx cell line
 - **McCoy** cell line: Human synovial carcinoma cell line (used for isolation of Chlamydia and viruses)
 - **Vero** cell line: Vervet monkey kidney cell line (used for rabies vaccine production)

- **BIHK** cell line: baby hamster kidney cell line
- **Detroit 6** cell line: sternal marrow cell line
- **Chang C/I/L/K** cell line: Human Conjunctiva, Intestine, Liver, Kidney cell line.

Detection of Viral Growth in Cell Line

- **Cytopathic effect:** Defined as the morphological change.

Type of cytopathic effect	Virus
Rapid crenation and degeneration of entire sheet	Enteroviruses
Cytoplasmic vacuolations	SV40 (Simian vacuolating virus-40)
Large granular clumps resembling bunch of grapes	Adenovirus
Syncytium or multinucleated giant cell formation	Measles, RSV, HSV
Diffuse rounding and ballooning of the cell line	HSV

Assay of Infectivity of Viruses

- **Physical methods:** These methods estimate the total virus count (or viral antigen or gene count) and cannot distinguish between infectious and non-infectious viral particles.
 - Real time PCR
 - Antigen detection assay
 - Electron microscopy
- **Biological methods:** Detects infectious virions. Examples include:
 - **Qualitative** assay (end point biological assays)
 - **Quantitative** assay (**plaque** assay, **pock** assay).

VIRAL INCLUSION BODIES

Intracytoplasmic	
Fowl Pox	Bollinger, Borrel's body
Molluscum contagiosum	Henderson Peterson body
Rabies	Negri bodies
Smallpox (vaccinia)	Guarnieri's bodies
Variola	Paschen bodies
Reovirus	Perinuclear cytoplasmic body
Intranuclear	
Cowdry type A	
Yellow fever	Torres body
Herpes viruses and varicella	Lipschutz body
Cowdry type B	Adenovirus, poliovirus
Both Intracytoplasmic and Intranuclear	
CMV	Owl eye inclusions
Measles	Warthin-Finkeldey

DNA VIRUSES

POXVIRUS

1. Variola (Smallpox), eradicated on 8th May 1980, threat in biological warfare
2. Vaccinia—an artificial virus; causes cowpox (milkmaid's blisters)
3. Molluscum contagiosum: MCV1 is most prevalent; causes pearly umbilicated nodule; inclusion bodies are called molluscum bodies are H-P (Henderson-Peterson) bodies.

PAPOVAVIRIDAE

1. Human Papilloma Virus (HPV) – causes
 - Cervical intraepithelial neoplasia and cervical cancer:
 - The International Agency for Research on Cancer concludes that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are carcinogenic in the uterine cervix.
 - HPV-16 is very virulent and causes 50% of cervical cancers. Worldwide, HPV-16 and HPV-18 cause 70% of cervical squamous cell carcinoma and 85% of cervical adenocarcinoma.
 - Anal cancers:
 - HPV-16 and HPV-18 also cause nearly 90% of anal cancers worldwide.
 - Warts: Mainly by HPV-6 and HPV-11. Types of warts:
 - Verruca vulgaris (MC type of wart)
 - Verruca plana (flat wart)
 - Superficial plantar wart (mosaic wart)
 - Deep plantar wart (myrmecia wart)
 - Condyloma acuminata (anogenital wart)
 - Laryngeal papillomatosis
 - Bowenoid papulosis
 - Epidermodysplasia verruciformis

- HPV vaccines:
 - Given to women between 9 and 26 years of age; has efficacy of > 90%.
 - Bivalent vaccine (Cervarix): Contains HPV types 16 and 18; given by IM injection at months 0, 1, and 6.
 - Quadrivalent vaccine (Gardasil): Contains L1 VLP (HPV-6, -11, -16, and -18) vaccine; given by IM injection at months 0, 2, and 6.
- 2. Polyomavirus
 - JC virus, BK virus and Merkel cell virus have been cultured from the urine of kidney transplant recipients in the setting of immunosuppression.
 - JC virus – progressive multifocal leukoencephalopathy (PML) in HIV patients.

Parvovirus

- Parvovirus B19 causes:
 - Aplastic crises in sickle cell disease
 - Slapped cheek rash-erythema infectiosum (fifth disease)
 - Hydrops fetalis
 - Purpuric gloves and socks syndrome on hands and feet

ADENOVIRUS

- Adenoviral diseases and the corresponding serotypes are as follows:
- Epidemic keratoconjunctivitis (shipyard eye/pink eye) by 8, 19, 37.
 - Pharyngoconjunctival fever (sore throat with pink eye) by 3, 7.
 - Hemorrhagic cystitis by 11, 21.
 - Pneumonia and acute gastroenteritis.
 - Hepatitis in liver transplant recipients.

HERPES VIRUSES

Virus	Infection
Varicella zoster virus (VZV), α herpes virus	Chickenpox Shingles (herpes zoster)
Cytomegalovirus (CMV), β herpes virus	Congenital infection In AIDS: pneumonitis, retinitis (cottage cheese and tomato ketchup retinopathy, Pizza pie retinopathy), enteritis, generalized infection; Basophilic intranuclear 'owl eye' inclusions

Contd...

Virus	Infection
Estein-Barr virus (EBV), γ herpes virus 'α, β, γ are Very Cunning Enemies'	Infectious mononucleosis Burkitt's lymphoma Nasopharyngeal carcinoma Oral hairy leukoplakia (AIDS patients)
Herpes simplex virus 1 (HSV1)	Herpes labialis (cold sores) Keratoconjunctivitis Finger infections (whitlow) Encephalitis Gingivostomatitis Genital infections
HSV2	Genital infections (more recurrence) Neonatal infections (acquired during vaginal delivery)
Human herpes virus 6 (HHV-6) and HHV-7	Exanthema subitum ??? disease in immunocompromised patients
HHV-8	A/w Kaposi's sarcoma

EXTRA EDGE

- Tzanck test: A smear of an opened skin vesicle to detect multinucleated giant cells. Used to assay for HSV-1, HSV-2, and VZV.

RNA VIRUSES

PICORNAVIRUSES

- They are divided into:
 - Enteroviruses: includes Poliovirus; Coxsackie virus A and B; Echovirus; Enterovirus (68-71) and Hepatitis A virus
 - Rhinovirus
- Feco-oral route is the usual mode of spread of enterovirus.

1. Poliovirus

- Three types exist:
 - Type 1, P1 (MC and causes most epidemics)
 - Type 2, P2
 - Type 3, P3 (a/w vaccine associated paralytic polio).
- Man is the only reservoir; no chronic carrier state exists.
- For every clinical case, there maybe 1000 subclinical cases in children and 75 cases in adults.
- In the feces, virus is excreted commonly for 2-3 weeks; sometimes as long as 3-4 months.
- Poliovirus spreads hematogenously and reaches the anterior horn of the spinal cord.
- Incubation period—7-14 days.
- The clinical types are as follows:
 - Subclinical (inapparent) infections: MC (95%).
 - Minor (abortive) illness

- Aseptic meningitis/nonparalytic polio
- Paralytic polio (<1%): there is flaccid paralysis with absent reflexes; respiratory paralysis is the MC cause of death.
- Paralysis is characterized by:
 - Descending paralysis
 - Affects proximal > distal muscles
 - No autonomic disturbance
 - Non-progressive
 - Asymmetrical
 - No sensory involvement
 - Lower motor neuron type.
- Risk of paralytic polio is increased by: tonsillectomy, adenoidectomy, tooth extraction, strenuous physical exercise, IM injection, fatigue and cortisone administration.
- Lab diagnosis: Based on viral isolation from feces samples taken 24-48 hours apart; serodiagnosis is not used.

2. Coxsackievirus

- Aseptic meningitis
- Summer gripe (infantile febrile illness)
- Acute epidemic hemorrhagic conjunctivitis (MC by A24) Herpangina (febrile pharyngitis)

- Hand, foot and mouth disease
- Infantile Myocarditis, pericarditis
- Epidemic pleurodynia (Bornholm disease)
 - Also caused by enterovirus 70, adenovirus 11)

3. Enterovirus

- Enterovirus 70-Acute hemorrhagic conjunctivitis
- Enterovirus 72-hepatitis A virus

4. Echovirus

- MC cause of Aseptic meningitis.

RHABDOVIRUS (RABIES VIRUS)

- Rabies virus (Lyssavirus serotype 1)
- Rabies is caused by dog bite.
- Virus has bullet-shaped capsid.
- Has long incubation period (weeks to months).
- Causes fatal encephalitis with seizures, hydrophobia, hypersalivation, and pharyngeal spasm.
- Negri bodies are characteristic intracytoplasmic inclusions in neurons of limbic system infected by rabies virus.
- Negri bodies are MC in hippocampus-Ammon's horn; ALSO seen in spinal cord (peripheral ganglia, basal ganglia); brainstem (pons, medulla); cerebral cortex; thalamus, cerebellum (Purkinje's cells).

ORTHOMYXOVIRUS

- Influenza virus; Genetic shift (pandemic) 'shlp, genetic drift (epidemic).
- Types: Type A (MC and causes all pandemics), Type B and Type C.
- Subtypes of influenza virus A:
 - H1N1 (causes swine flu)

OTHER RNA VIRUSES

Viral family	Medical importance
Caliciviruses	<ul style="list-style-type: none"> • HEV – acute viral hepatitis, high mortality in pregnant women • Norwalk virus – gastroenteritis associated with undercooked seafood
Reoviruses	<ul style="list-style-type: none"> • Reovirus – Colorado tick fever • Rotavirus – MC cause of diarrhea in children; Villous destruction with atrophy leads to ↓ absorption of Na and water; genetic reassortment in rotaviruses produces more virulent strains.
Flavivirus	<ul style="list-style-type: none"> • HCV • Yellow fever (arbovirus), Flavi = yellow; transmitted by Aedes mosquito; Symptoms: high fever, black vomitus, and jaundice. Councilman bodies (acidophilic apoptotic inclusions; also seen in acute viral hepatitis) may be seen in liver; yellow fever NOT IN INDIA. • Dengue (arbovirus) • West Nile virus (arbovirus)

- H5N1 (causes bird flu)
- H7N9 (caused epidemic of bird flu in China in 2013)
- Contain hemagglutinin and neuraminidase antigens. Responsible for worldwide influenza epidemics; patients at risk for fatal bacterial superinfection.
- Elution is seen (detachment of virus from cell surface resulting hemagglutination).
- Amantadine and rimantadine useful for influenza A (especially prophylaxis). High level of resistance to these drugs; NO longer used.
- Zanamivir and oseltamivir (neuraminidase inhibitors) useful for both influenza A and B.

PARAMYXOVIRUS

1. Parainfluenza—MC cause of croup
2. Respiratory Syncytial Virus (RSV)—MC cause of bronchiolitis in babies, treat with ribavirin or palivizumab, F (fusion)-protein leads to syncytium formation.
3. Measles (Rubeola): full details in pediatrics chapter (Pg 691).
4. Mumps (causes parotitis and orchitis as complication)
 - Man is the only natural host.
 - Transmitted as droplets infection.
 - Period of infectivity (communicability) is 4-6 days before the onset of symptom to a week thereafter.
 - Secondary attack rate is 86%.
 - Incubation period is 2-3 weeks.
 - Clinically, presents with parotitis.
 - Orchitis is the MC complication among postpubertal males.
 - Overall, aseptic meningitis is the MC complication.
 - Mumps vaccine is a live attenuated vaccine, prepared from Jeryl Lynn strain.
 - One clinical attack of mumps also confers lifelong immunity.

Contd...

Contd

Viral family	Medical importance
Togaviruses	<ul style="list-style-type: none"> • Rubella (german measles); full details in pediatrics chapter (Pg 693)
Retroviruses	<ul style="list-style-type: none"> • Have reverse transcriptase • HIV – AIDS • Human T cell Leukemia Virus (HTLV) – T cell leukemia
Coronaviruses	<ul style="list-style-type: none"> • Coronavirus – Common cold and Severe Acute Respiratory syndrome (SARS)
Filovirus	<ul style="list-style-type: none"> • Ebola/Marburg hemorrhagic fever
Arenavirus	<ul style="list-style-type: none"> • LCV – lymphocytic choriomeningitis virus
Bunyavirus	<ul style="list-style-type: none"> Rift valley fever Hantavirus

SUMMARY OF HEPATITIS VIRUSES

Name	Viral characteristics	Transmission	Special features
Hepatitis A (infectious hepatitis)	Icosahedral Non-enveloped ssRNA Family: picornaviridae; enterovirus 72; genus: hepatovirus	Fecal-oral, food borne	<ul style="list-style-type: none"> • IP = 15-45 days (mean 30) • Onset usually abrupt, disease mild, self limiting • NO chronic infection, NOT a/w cancer • Vaccine: Immunoglobulin, inactivated vaccine available • Prognosis: Excellent • Treatment: None
Hepatitis B (serum hepatitis)	Spherical Enveloped dsDNA Family: Hepadnaviridae	Parenteral (MC), sexual or vertical transmission	<ul style="list-style-type: none"> • IP = 30-180 days (mean 60-90) • Insidious onset common • A/w primary hepatocellular carcinoma (HCC), cirrhosis, PAN • Maximum chance of HCC and perinatal transmission • Vaccine available-HBIG, recombinant vaccine • Prognosis: worse with age • Treatment: Interferon, Lamivudine, Adefovir, Pegylated interferon, Entecavir, Telbivudine, Tenofovir
Hepatitis C (post transfusion hepatitis, parenterally transmitted Non-A, Non-B hepatitis virus)	Spherical Enveloped ssRNA Family: Flaviviridae; genus: Hepacivirus	Parenteral (MC); vertical or sexual transmission (+/-)	<ul style="list-style-type: none"> • IP = 15-160 days (mean 50) • Insidious onset common • Acute disease is usually subclinical • High rate of chronicity (85%) • A/w primary hepatocellular carcinoma, cirrhosis, cryoglobulinemia • Maximum chances of chronic hepatitis and carrier state • Vaccine: NO vaccine • Prognosis: moderate • Treatment: Pegylated interferon plus ribavirin, telaprevir, boceprevir
Hepatitis D (delta hepatitis)	Spherical Enveloped ssRNA Defective enveloped hybrid particle with HBsAg coat and HDV core Resembles plant virioids (Genus: deltavirus)	Coinfection or superinfection with HBV	<ul style="list-style-type: none"> • IP = 30-180 days (mean 60-90) • Insidious onset common • A/w fulminant hepatitis • Coinfection (both acquired at same time) is occasionally severe • Superinfection (patient already infected with B, then acquires B and D) has high mortality • Vaccine: HBV vaccine • Prognosis: Acute-good; chronic-poor • Treatment: Pegylated interferon
Hepatitis E (Enteric nontransmitted Non-A, Non-B hepatitis virus)	Icosahedral Non-enveloped ssRNA Family: Hepeviridae; genus: hepevirus; resembles: Caliciviridae	Fecal-oral, food borne	<ul style="list-style-type: none"> • IP = 14-60 (mean 40) • Severe and high 20% mortality in pregnant patients • NO chronic infection, NOT a/w cancer • Vaccine (HEV239) only in China • Treatment: None • MC cause of acute sporadic and epidemic viral hepatitis in India (HEV genotype 1)

Mnemonics for Hepatitis

- A and E feco-oral: 'The vowels hit your bowels'
- Hepatitis A: Asymptomatic (usually), Acute, Alone (no carriers).
- Hepatitis B: Blood borne.
- Hepatitis C: Chronic, Carriers.
- Hepatitis D: Defective, Dependant on HBV.
- Hepatitis E: Expectant mothers, Epidemics.

HEPATITIS B VIRUS

Structure of HBV

- **Dane particle** (42 nm): It is the complete hepatitis B virus and contains three antigens—(1) core antigen or HBcAg, (2) surface antigen or HBsAg and (3) e antigen or HBeAg.
- **Spherical particle** (22 nm): This is MC and is exclusively the HBsAg.
- **Tubular/filamentous** form (200 nm long)-exclusively made up of HBsAg.

HBV Genome

Genes	Regions	Gene products
S	S	Major Protein S (HBsAg)
	S + pre-S2	Middle protein (M)
	S + pre-S2 + S1	Large protein (L)
C	C	HbcAg
	C+ pre-C	HbeAg
P (largest gene)		DNA polymerase
X		HbxAg

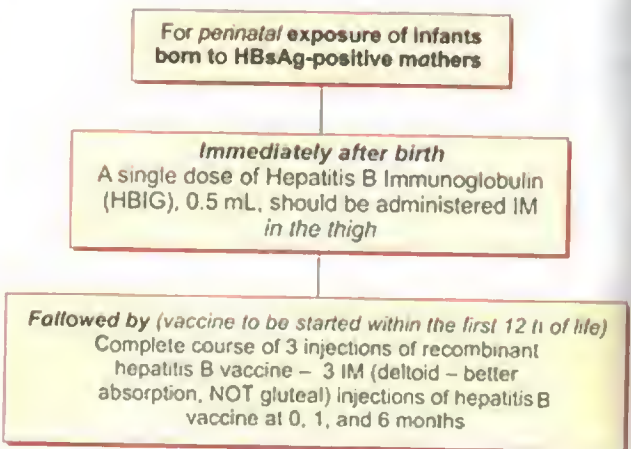
Hepatitis B Virus Mutants

- **Precore mutants:** They have defect in precore region of C gene which leads to their inability to synthesis HBeAg, i.e. HBeAg is absent.
- **Escape mutants:** They have mutations in the S gene—leads to alterations of HBsAg (usually in alpha antigen). ('S-cape mutants-S gene-altered HBsAg'). They may pose problems in hepatitis B vaccination strategies as well as in the diagnosis of the disease. These mutations are observed in:
 - Infants born to HBsAg positive mothers
 - Liver transplant recipients
 - A small proportion of recipients of active and passive immunization.
- **YMDD mutation:** HBV infected patients on lamivudine therapy may develop resistance due to mutation in the

YMDD locus present on reverse transcriptase region of P gene of HBV.

Hepatitis B Prophylaxis

- **Passive prophylaxis:** Hepatitis B immunoglobulin.
- **Active immunization:** recombinant hepatitis B vaccine (Engerix B, etc.)
- Vaccine is given **IM** into **deltoid**-NOT gluteal (or into anterolateral thigh in infants).
- Three doses are give at **0, 1 and 6 months**.
- For **pre-exposure prophylaxis** only hepatitis B vaccine is given.
- **Post-exposure prophylaxis.**
- For direct percutaneous inoculation or transmucosal exposure to HBsAg-positive blood or body fluids (e.g. accidental *needlestick*, other mucosal penetration, or ingestion) - A **single IM dose of HBIG**, 0.06 mL/kg, administered **as soon after exposure as possible**, followed by a **complete course of hepatitis B vaccine** to begin **within the first week**.
- For those exposed by **sexual contact** to a patient with **acute hepatitis B** - A **single IM dose of HBIG**, 0.06 mL/kg, should be given **within 14 days of exposure**, to be followed by a **complete course of hepatitis B vaccine**.
- For perinatal exposure see flowchart below.
- Pregnancy is **NOT** a contraindication to vaccination.
- When both HBIG and hepatitis B vaccine are recommended, they **may be given at the same time BUT AT separate sites**.
- **Universal vaccination of neonates in countries endemic for HBV** has reduced the incidence of hepatocellular carcinoma.
- Vaccine formulations **free of the mercury-containing preservative thimerosal** are given to infants < 6 months of age.



Hepatitis B Serology

HBsAg (surface antigen or Australia antigen)	<ul style="list-style-type: none"> • First virologic marker detectable in serum after infection with HBV (appears at 8–12 weeks). • Indicates active hepatitis B infection, either acute or chronic (> 6 months) • Epidemiological marker of HBV infection (i.e. to calculate prevalence of infection)
Anti-HBs	<ul style="list-style-type: none"> • After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter • Its presence indicates immunity, recovery and non-infectivity (i.e. stoppage of transmission) of hepatitis B. It is a protective antibody • It is the ONLY marker of vaccination
HBcAg (core antigen)	<ul style="list-style-type: none"> • NOT routinely detectable in blood (because HBcAg is a hidden antigen due to surrounding HBsAg coat) • HBcAg may be detected in hepatocytes by immunofluorescence
Anti-HBc	<ul style="list-style-type: none"> • First antibody to appear; Positive during the window period. • IgM anti-HBc is an indicator of acute infection/recent disease (< 6 months). • IgG anti-HBc signifies chronic infection/remote disease. • Anti-HBc is readily demonstrable in serum, beginning within the first 1–2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months.
HBsAg (envelope antigen)	<ul style="list-style-type: none"> • Indicates active viral replication and high infectivity. ('Beware!') • Qualitative marker of HBV replication (Note: HBV DNA is a quantitative marker of HBV replication).
Anti-HBe	<ul style="list-style-type: none"> • Its presence signifies diminished viral replication and decreased infectivity.

HEPATITIS C VIRUS ESSENTIALS

- Among hepatitis viruses, **HCV** has maximum propensity for **chronic hepatitis and carrier state**.
- **MC indication for liver transplantation** is cirrhosis due to **chronic HCV infection**.
- HCV usually does NOT cause acute liver failure (rare).
- **Extrahepatic manifestation** with HCV are essential mixed cryoglobulinemia, porphyria cutanea tarda, pulmonary fibrosis, lichen planus and membranoproliferative glomerulonephritis.
- **Most sensitive test** for establishing diagnosis is assay for **HCV RNA**
- Anti-HCV antibodies may **never** be detectable in 5–10% patients with acute hepatitis C.

Drugs Approved for Treatment of Hepatitis B and C

Hepatitis B	Hepatitis C
<ul style="list-style-type: none"> • Lamivudine, Telbivudine • Adefovir, Tenofovir • Entecavir • Pegylated interferon (SC injection) • Interferon-alpha (no longer used) 	<ul style="list-style-type: none"> • Pegylated Interferon (alfa 2A more effective, given SC) plus Ribavirin (orally)-DOC • Protease inhibitor: Boceprevir, Telaprevir, Simeprevir, Paritaprevir • Polymerase inhibitor: Sofosbuvir • HCV NS5A inhibitor: Ombitasvir, Ledipasvir • HCV NS5B inhibitor: Dasabuvir

MYCOLOGY

- Morphological Classification of Fungi and Superficial Skin Infections - Dermatophytosis are covered under **dermatology** chapter (Pg 1068).
- Dimorphic fungi:
 - Histoplasma capsulatum
 - Blastomyces dermatitidis
 - Sporothrix schenckii
 - Coccidioides immitis
 - Paracoccidioides brasiliensis
 - Penicillium marnefei
- (It's **Blasted Sports Car Party Pen**).

DEEP FUNGAL INFECTIONS

Candida

- Candida is a **yeast-like fungus**.
- Common normal flora but opportunistic pathogen; **budding yeast with pseudohyphae** in culture at 20°C; **germ tube** formation at 37°C diagnostic—**Reynolds-Braude phenomenon**.
- Transmission occurs by **inhalation of spores**.
- No person-to-person spread.
- **Candida albicans** is differentiated from other candida by **true hyphae (mycelia)** and **chlamydospores**.

- *Candida* is the **MC fungal infection** in immunocompetent people as well as neutropenic patients.

Candidal diseases (candidiasis)

- **Oral Thrush, perleche** (at angle of mouth), **esophagitis** in immunocompromised (neonates, steroids, diabetes, AIDS)
- **Vulvovaginitis** (high pH, pregnancy, diabetes, use of antibiotics)
- Chronic mucocutaneous candidiasis (ass. with T-cell deficiency)
- **Endocarditis** in IV drug users (caused by *Candida parapsilosis* and *Candida tropicalis*), paronychia
- Disseminated candidiasis (to any organ)
- **Intertrigo** in skin folds

Cryptococcosis (Cryptococcus Neoformans)

- The **only pathogenic yeast**; has **polysaccharide capsule**.
- **Four capsular serotypes** exist (A, B, C, D):
 - Most infections in **immunocompromised** are caused by **type A**.
 - **Pigeon droppings** contain serotype **A and D**.
 - **Eucalyptus tree** contains serotype **B**.
- It is **urease positive**.
- Yeast with large capsule seen on **India ink stain**; **mucicarmine stain in tissues**; culture on Sabouraud's agar.
- Latex agglutination (**most rapid and sensitive test**) test detects **polysaccharide capsular antigen**.
- Acquired by **inhalation** of fungus into the lungs; found in **soil, pigeon droppings**.
- **Cryptococcal meningitis** in immunosuppressed, **MC in AIDS**; small cysts in gray matter of brain—'**Soap bubble**' lesions.
- **Torulosis** is cryptococcal CNS infection.
- **European blastomycosis** is caused by *Cryptococcus*.
- Other lesions are pulmonary, skin (**umbilicated papules** in AIDS patient may resemble molluscum!), osteolytic (presenting as cold abscess), prostatitis, endophthalmitis, hepatitis, pericarditis, endocarditis and renal abscess.
- Treatment: Amphotericin, then fluconazole for life for prophylaxis.

Histoplasmosis

- **Intracellular** (tiny yeast inside macrophages); also called **Darling's disease**.
- Acquired via **inhalation** of spores in **bat guano or bird droppings**.
- Causes:
 - Pneumonia, chronic pulmonary histoplasmosis.
 - Sputum culture is the preferred method for diagnosis

- Presumed ocular histoplasmosis syndrome.
- Treatment: Itraconazole for pneumonia, **amphotericin B** for disseminated disease.

Mucormycosis

- Mold with irregular nonseptate hyphae branching at wide angles (> 90°).
- Frequent causes are **Mucor, Rhizopus, Absidia and Cunninghamella**.
- Fungi also proliferate in the walls of blood vessels and cause **infarction and necrosis of distal tissue**.
- Disease mostly in **ketoacidotic diabetics, organ transplant patients** and leukemic patients.
- Types:
 - **Rhinocerebral**—Can start as headache or visual loss, starts in paranasal sinuses, spreads to orbit (proptosis), CN III palsy, hard palate, brain (frontal lobe abscess).
 - **Pulmonary and cutaneous** mucormycosis
- **Treatment: Surgical debridement plus amphotericin B.**

Coccidioidomycosis

- *Coccidioides immitis* reproduces in host tissue by forming small **endospores** within mature **spherules**. It forms thick-walled, **barrel-shaped spores (arthrospore)**. Infection results from inhalation of arthrospores.
- Causes
 - A self-limited influenza like fever (**valley fever**) with arthralgia (**desert rheumatism**), and erythema nodosum
 - Disseminated disease—pneumonia and meningitis may occur.
- Treatment: Amphotericin B, fluconazole, itraconazole

Blastomycosis (North American Blastomycosis)

- Caused by *Blastomyces dermatitidis* characterized by the formation of suppurative and granulomatous lesions in any part of the body, but with a marked predilection for the lungs and skin.
- **Pseudoepitheliomatous hyperplasia** may be striking and lead to a mistaken diagnosis of squamous cell carcinoma.

Paracoccidioidomycosis (South American Blastomycosis)

- Progressive pulmonary disease; skin lesions and cervical lymphadenopathy.
- **Ulcerative granulomas of the buccal and nasal mucosa** are a prominent feature of the disease.
- CXR most often shows bilateral patchy pneumonia.

Aspergillosis

- **Aspergillus fumigatus (MC)**, *A. niger*, *A. flavus*; mold with septate hyphae that branch at a V-shaped (45°) angle.

Diseases:

- **Aspergilloma ('fungus ball')** in an old (usually tuberculous) lung cavity, causes hemoptysis, rarely becomes invasive.
- Invasive pulmonary aspergillosis, (in neutropenic patients, leukemics, and chronic granulomatous disease)
- Disseminated disease: in patients on chronic steroids, neutropenics.
- **Onychomycosis (*A. niger* MC)**, corneal ulcers.
- *A. flavus* produces **mycotoxin (aflatoxin B1)**
- Treatment: amphotericin B, itraconazole, voriconazole.

Allergic bronchopulmonary aspergillosis (ABPA)

- A hypersensitivity reaction to *A. fumigatus* (MC) occurs in patients with preexisting asthma who develop worsening bronchospasm and fleeting pulmonary infiltrates accompanied by eosinophilia, high levels of IgE (> 1000 IU/mL)
- IgG Aspergillus antibodies in the blood
- A positive skin-prick test in response to *A. fumigatus* extract
- Presence of hyperattenuated mucus in airways is highly specific central bronchiectasis is characteristic

SUBCUTANEOUS MYCOSES

Maduramycosis (Mycetoma)

- Is a localized **chronic granulomatous** involvement of the subcutaneous and deeper tissues, commonly affecting the **foot** and less often the hand and other parts.
- Presenting as a subcutaneous swelling with **multiple discharging sinuses**.
- Sinuses discharge seropurulent fluid containing **granules**.
- These granules are microcolonies of the etiological agents
- Mycetoma can be caused by **both fungus and bacteria**.

Eumycetoma (Mycetoma caused by Fungus)

- It is caused by subcutaneous infection of fungi. Based on the color of granules in discharge these may be divided into:
 - **Black grain Mycetoma**: Caused by *Madurella mycetoma*, *Madurella grisea*, *Exophiala jeanselmei*, *Curvularia geniculata*.
 - **White grain mycetoma**: Caused by *Pseudallescheria boydii*, *Aspergillus nidulans*, *Fusarium*, *Acremonium*.

Actinomycetoma (Mycetoma caused by Bacteria)

- It is caused by *Actinomyadura madurae* (MC cause to India), *Actinomyces*, *Nocardia*, *Streptomyces* and *Allescheria boydii*. Color of granules is white to yellow. *Actinomyadura pelletieri* produces red granules.

Botryomycosis

- It is mycetoma like discharging lesion (but not a mycetoma), caused by *Staphylococcus aureus*.

Clinical Features

- Commonly occurs in **foot**.
- The infection runs as relentless course many years, with destruction of contiguous bone and fascia.
- Spread to distant sites does not take place (does not drain through lymphatics).
- Actinomycetoma may respond to prolonged combination chemotherapy, e.g. streptomycin and dapsone.

Treatment

- **Eumycetoma**: It is rarely respond to medical therapy. Some cases of madurella may respond to ketoconazole or itraconazole. In advanced and uncontrollable disease, amputation may be required.
- **Actinomycetoma**: It is treated by antibiotics like streptomycin plus dapsone or streptomycin plus cotrimoxazole.

EXTRA EDGE

- Superficial fungal infections (dermatophytoses) have been covered under dermatology chapter (Pg 1068).

Chromoblastomycosis

- **Chromoblastomycosis** is a **chronic, tropical subcutaneous** infection usually affecting **young men** who are **agricultural workers**.
- It is caused MC by two closely related **black molds**; *Cladophialophora carrionii* and *Fonsecaea pedrosoi*.
- **Warty/verruroid** lesions of lower extremities are seen.
- **Sclerotic cells**, also known as '**copper pennies**' or **Medlar bodies**, are globe-shaped, cigar-colored, thick-walled structures.

Sporotrichosis (Sporothrix Schenckii)

- Dimorphic fungus that lives on vegetation; cigar-shaped budding yeast visible in pus; '**asteroid bodies**' are seen on histology of the lesion.
- Infection is acquired through **thorn pricks ('rose gardener's disease')** or other minor skin trauma.
- Causes
 - **Plaque sporotrichosis**: Infection limited to the site of inoculation.
 - **Lymphangitic sporotrichosis**—more common, infections extends **along proximal lymphatic channels**, **skip areas** seen, spread beyond the regional lymph nodes is uncommon. Most cases occur in the **upper limb**.
- Treat with itraconazole or potassium iodide.

Parasitology

HISTORY

- Dutch microscopist, **Antoni van Leeuwenhoek of Holland in 1681**, first introduced single lens microscope and observed Giardia in his own stools!!
- Patrick Manson** in 1878, discovered the role of mosquitoes in Filariasis - this was the **first evidence of vector transmission**.
- Laveran in Algeria discovered the malarial parasite** in 1880.
- Ronald Ross** showed **transmission of malaria** by mosquitoes in 1897.

Classification of living organisms

The living organism are classified into 5 major kingdom:

- Prokaryotes-Monera (e.g. Bacteria, Blue green algae, archaeobacteria)
- Eukaryotes
 - Protista (e.g. Protozoal parasites)
 - Fungi (e.g. fungus)
 - Plantae (e.g. Plants)
 - Animalia (e.g. Helminths, arthropods and higher animals)

Host-parasite relationships

Symbiosis

- Both host and parasite are dependent upon each other
- None of them suffers any harm from the association

Commensalism

- Only the parasite derives benefit from the association without causing any injury to the host
- A commensal is capable of living an independent life also

Parasitism

- The parasite derives benefits and the host is always harmed due to the association
- The parasite cannot live an independent life

Life Cycle of Parasites

- Direct Life Cycle:** When a parasite requires only **single host** to complete its life cycle, it is called as direct life cycle.
- Indirect life cycle:** When a parasite requires **two or more species** of host to complete its development, its life cycle is called as indirect life cycle.

Parasites having direct life cycle (requiring no intermediate host)

Protozoa	Helminths
<ul style="list-style-type: none"> Entamoeba histolytica Giardia lamblia Trichomonas vaginalis Balantidium coli 	<ul style="list-style-type: none"> Ascaris lumbricoides Enterobius vermicularis Trichuris trichura Ancylostoma duodenale Necator americanus Hymenolepis nana

Parasites having indirect life cycle (requiring one intermediate and one definitive host)

Parasite	Definitive host	Intermediate host
Protozoa		
Plasmodium Spp.	Female anopheles mosquito	Man
Babesia	Tick	Man
Leishmania	Man, dog	Sandfly
Trypanosoma brucei	Man	Tsetse fly
Trypanosoma cruzi	Man	Triatomine bug
Toxoplasma gondii	Cat	Man
Cestodes		
Taenia solium	Man	Pig

Contd.

Parasites having indirect life cycle (requiring one intermediate and one definitive host)

Trichuris trichura	Man	Cattle
Leishmania	Dog	Man
Nematodes		
Clonorchis sinensis	Man	Snail
Parascaris	Man, pig	Snail
Plasmodium	Man	Snail
Nematodes		
Trichinella spiralis	Man	Pig
Wuchereria bancrofti	Man	Mosquito
Brugia malayi	Man	Mosquito
Strongyloides stercoralis	Man	Cyclops

Parasites with man as intermediate or secondary host

- Babesia spp.
- Plasmodium spp.
- Taenia solium
- Echinococcus granulosus and multilocularis
- Spirometra spp.
- Toxoplasma gondii
- IP TEST!**

Parasites having indirect life cycle requiring TWO intermediate and one definitive host

Parasite	Intermediate hosts	Definitive Host
Clonorchis spp.	Snail, plant	Man
Diphyllobothrium latum	Cyclops, Fish	Man
Clonorchis sinensis	Snail, Fish	Man
Paragonimus westermani	Snail, crustacean	Man

Parasites Causing Autoinfection

- Capillaria philippinensis, Cryptosporidium parvum
- Hymenolepis nana
- Enterobius vermicularis
- Strongyloides stercoralis
- Taenia solium
- Mnemonic: "**CHEST**"

Parasites causing Bloody Diarrhea

- Balantidium coli
- Entamoeba histolytica
- Intestinal Schistosomes: S. japonicum; S. mansoni; S. intercalatum; S. mekongi

- Trichuris trichura
- Mnemonic: "**BEST**"

Parasites Found in Peripheral Blood Film

Protozoa	Nematodes
<ul style="list-style-type: none"> Plasmodium Babesia Trypanosoma Leishmania 	<ul style="list-style-type: none"> Wuchereria bancrofti Brugia malayi Loa Loa Mansonella

Parasites Found in Urine

- Schistosoma hemotabium
- Wuchereria bancrofti
- Trichomonas vaginalis.

Parasites Causing Myocarditis

- Trypanosoma brucei and cruzi
- Toxoplasma
- Trichinella
- Echinococcus
- Mnemonic: "These parasites **Try To Trick** your ECG!"

Obligate Intracellular Parasites

- Plasmodium
- Babesia
- Leishmania
- Trypanosoma
- Toxoplasma
- Microsporidia.

Parasites Vertically Transmitted

Transmitted from *mother to fetus*

- Plasmodium
- Toxoplasma
- Trypanosoma

Acid-fast Parasites

- Microsporidia (spore)
- Cyclospora (oocysts)
- Isospora belli (oocyst)
- Cryptosporidium (oocyst)

Charcot-Leyden Crystals

Charcot-Leyden crystals are formed from the breakdown of eosinophils and may be seen in the stool or sputum of patients with parasitic disease. Seen in:

- Entamoeba histolytica
- Ascaris lumbricoides
- Trichuris infections.

Parasites Exhibiting Antigenic Variation

- Trypanosoma
- Plasmodium
- Giardia.

TESTS FOR PARASITES

Antigen detection in parasitic diseases

- Galactose lectin antigen: Entamoeba histolytica
- Giardia specific antigen 65: Giardia lamblia
- WKK and rk39 antigen: Leishmania donovani
- HRP-2 antigen: Plasmodium falciparum
- Vivax specific pLDH: Plasmodium vivax
- 200 kD Ag and OG4C3 antigen: Wuchereria bancrofti

Skin Tests for Parasites

Test	Parasitosis
Sabin Feldman dye test	Toxoplasmosis
Frenkel's skin test	Toxoplasmosis
Casoni's skin test	Hydatid cyst
Montenegro or Leishmanin skin test	Leishmaniasis
Scotch tape test	Enterobiasis (Pinworm)
Fairley's skin test	Schistosomiasis
Skin snip test	Onchocerciasis
Bachman's intradermal test	Trichinellosis

EGGS

Eggs Which Do NOT Float in Saturated Salt Solution

- Strongyloides larva.
 - Unfertilised egg of Ascaris lumbricoides (heaviest of all helminthic eggs)
 - Intestinal flukes eggs all.
 - T. saginata and T. solium eggs
- Mnemonic: "SUITcase (filled with eggs will NOT float)!"

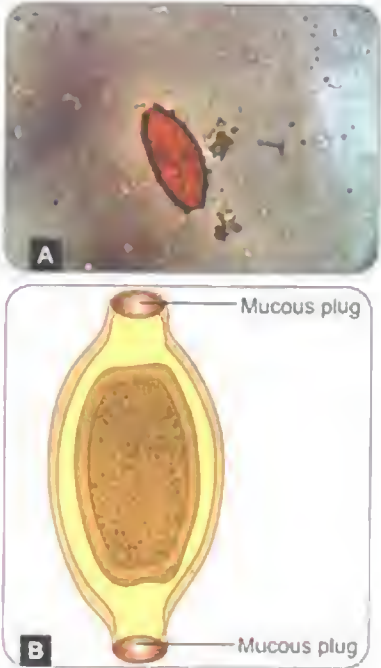
Bile Staining of Eggs

Bile stained (Colored)	Not bile stained (Colorless)
• Trichuris	• Hookworm (Ancylostoma, Necator)
• Ascaris	• E. vermicularis
• Taenia	• H. Nana
• Clonorchis sinensis	
• Fasciola hepatica	
• Fasciolopsis buski	

Mnemonic: "They Are Too Color Full!"

Schistosome Eggs

- Egg with Terminal Spine: *S. haematobium* (TSH!)
- Egg with Lateral Spine: *S. mansoni*
- Egg with Lateral Knob: *S. japonicum* (IKL)



Figs. 6.1A and B: Egg of Trichuris trichiura. A. As seen under microscope; B. Schematic diagram

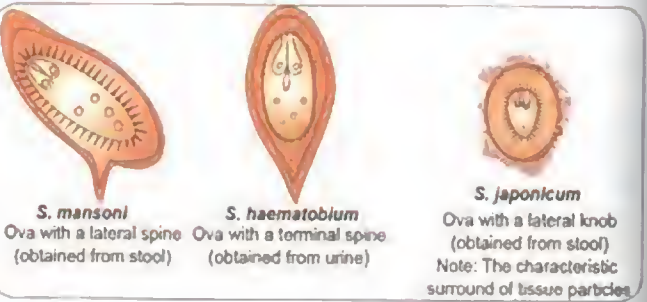


Fig. 6.2: Schematic diagram to show distinguishing features of eggs of S. mansoni, S. haematobium, and S. japonicum

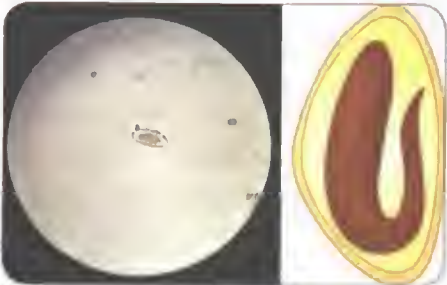
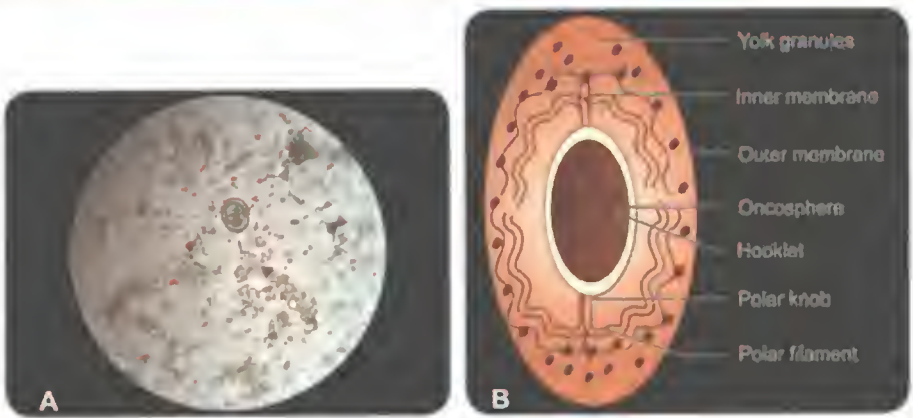


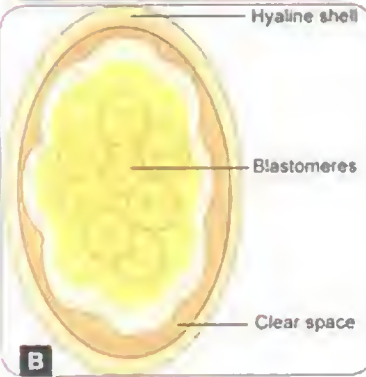
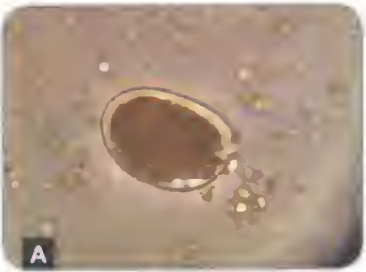
Fig. 6.3: Planoconvex egg of enterobius vermicularis is containing tadpole-shaped embryo



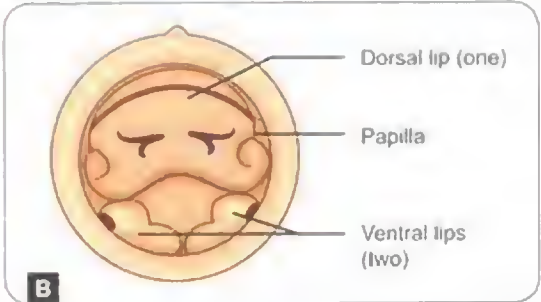
Figs. 6.4A and B: Egg of hymenolepis nana. (A) As seen under microscope; and (B) Schematic diagram



Fig 6.5: Egg of fasciola hepatica



Figs. 6.6A and B: Egg of ancylostoma duodenale. A. As seen under microscope; B. Schematic diagram



Figs 6.7A and B: A. Unfertilized egg of Ascaris; B. Anterior end of worm.

Parasites with Operculated Eggs

- Fasciola hepatica and gigantica
- Fasciolopsis buski
- Clonorchis sinensis
- Paragonimus westermani
- Gastrodiscoid hominis
- Opisthorchis spp.
- Heterophyes heterophyes
- D. latum (only cestode with operculated egg!)

HELMINTHS: GENERAL FEATURES

	Cestodes	Trematodes	Nematodes
Phylum	Platyhelminthes	Platyhelminthes	Nematoelminthes
Shape	Tape-like, segmented	Leaf-like; unsegmented	Elongated, cylindrical, unsegmented
Sexes	Not separate, i.e., hermaphrodite (monoecious)	Not separate, i.e., hermaphrodite (monoecious), except schistosomes which are diecious	Separate (diecious)
"Head" End	Suckers, often with hooks	Suckers, NO hooks	NO suckers, NO hooks Well developed buccal capsule in some species
Alimentary canal	Absent	Present but incomplete no anus	Present and complete anus present
Body cavity	Absent	Absent	Present
Life cycle	Requires two hosts except Hymenolepis (one host) and Diphyllbothrium (three hosts)	Requires three hosts except schistosomes (two hosts)	Requires one host except filarial worms (two host) and Dracunculus (two host)
Some Examples	Taenia (tapeworms); E. chinococcus; Hymenolepis; Diphyllbothrium	Flukes: Blood flukes (schistosomes) and other flukes	Roundworms, Hookworms etc.

HELMINTHS: CESTODES (TAPEWORMS)

Classification of Tapeworms

- Phylum *Platyhelminthes*
 - Order *Pseudophyllidea*: Genus *Diphyllbothrium* and *Spirometra*
 - Order *Cyclophyllidea*: Genus *Taenia*, *Echinococcus*, *Hymenolepis* and *Dipylidium*

Alternate names of tapeworms

- Fish tapeworm : *Diphyllbothrium latum* (**Longest**)
- Beef tapeworm : *Taenia saginata*
- Pork tapeworm : *Taenia solium*
- Dwarf tapeworm : *Hymenolepis nana* (**MC and smallest**)
- Rat tapeworm : *H. diminuta*
- Dog tapeworm : *Echinococcus granulosus*
- Double pored dog tapeworm : *Dipylidium caninum*

EXTRA EDGE

- Mnemonic:** How to remember which is saginata and which is solium? The word "saginata" is larger than the word "solium" JUST LIKE Cow is larger than Pig! Thus saginata = beef/cow tapeworm and solium = pork tapeworm.

Taenia Saginata Versus Taenia Solium

	Taenia Saginata (Beef tapeworm)	Taenia Solium (Pork tapeworm)
Description	Larger (5–10 m); Unarmed (NO rostellum, hooks)	Smaller than T.saginata (2–3 m); Armed (HAS rostellum and hooks)
Definitive host	Man	Man
Intermediate host	Cow	Pig; occasionally man (in case of cysticercosis)
Mode of infection	Ingestion of undercooked (measly) beef containing cysticercus bovis (larval form)	Ingestion of undercooked (measly) pork containing cysticercus cellulosae (larval form); autoinfection and eggs in contaminated vegetable, food and water
Eggs	Not infective to human	Are infective to human
Clinical features	Intestinal taeniasis only; usually asymptomatic; occasionally include abdominal discomfort and indigestion.	Adult worm is asymptomatic. Larval forms cause cysticercosis : lesions in subcutaneous tissue, muscle, eye and brain (neuracysticercosis)

Contd.

Contd.

	Taenia Saginata (Beef tapeworm)	Taenia Solium (Pork tapeworm)
Diagnosis	Eggs or proglottids in stool; molecular diagnosis; serodiagnosis	Eggs or proglottids in stool for intestinal taeniasis; For cysticercosis: Biopsy, X-ray, CT, MRI
Treatment	Praziquantel is the DOC	For intestinal taeniasis: Praziquantel For neurocysticercosis: Albendazole is DOC; anti-epileptics (for seizures) and corticosteroids (for reducing inflammation caused by dead cysticerci)
Prophylaxis	Avoid eating undercooked beef	Avoid eating undercooked pork and raw vegetables

- Eggs of T.saginata and T.solium are **indistinguishable**.
- Cysticercus cellulosae is also called '**bladder worm**'.
- Neurocysticercosis is the MC form of cysticercosis; can cause '**rice grain**' calcification in brain
- About **70% of adult onset seizures** in India is due to neurocysticercosis.
- ELISA for **coproantigen** in feces is used for detecting taenia (It is MORE sensitive than microscopy BUT cannot distinguish between saginata and solium!).
- Fischer's** 4 pathological stages are used for classifying neurocysticercosis.

Taenia Saginata Asiatica

- Seen mainly in Asia.
- Morphologically similar to T.saginata except
 - Smaller than T.saginata
 - Intermediate host is **pig** (not cow!).
 - Its cysticerci are located in **liver** of pig (not muscle!).
- Clinical features and treatment similar to T.saginata.

Taenia Multiceps (Multiceps multiceps)

- Natural parasites of **dogs** and other canines (wolf, fox) - definitive hosts.
- Intermediate hosts: Sheep, cattle, horses.
- Man acts as accidental intermediate host.
- Larval stage is called **coenurus** - causes coenuriasis.
- In sheep it causes cerebellar ataxia—disease called as '**staggers**'.

Echinococcus Granulosus

- A **canine** tapeworm; seen in **temperate** climates.
- Smaller than other tapeworms (**3–6 mm**); has a **pyriform** scolex.
- Definitive host: Dog (optimal host)**; wolf; jackal; fox.
- Intermediate host: Sheep (ideal)** and cattle.
- Man acts as an **accidental intermediate host** (dead end).
- Mode of infection:** Ingestion of eggs in food items contaminated with dogs feces.

- Causes **hydatid cyst**; MC in **liver** (first filter) > lung (second filter).

Layers of Hydatid Cyst

- Pericyst** (composed of inflammatory material)
- Ectocyst** (acellular laminated chitinous material) and
- Endocyst** (the germinal layer which gives rise to new brood capsules and scolices and hydatid fluid).

- Hydatid fluid** is acidic (pH 6.7); contains salts and proteins; is **antigenic** and **highly toxic**; it was used as antigen for **Casoni's intradermal test**.
- Hydatid cyst has been discussed further in **surgery chapter** and in **radiology chapter** (signs of pulmonary hydatid cyst) (Pg 897, 1173).
- Water Lily sign:** Due to detached endocyst floating within the cyst cavity.
- Casoni's intradermal skin test:** Immediate (type 1) hypersensitivity reaction to fresh sterile hydatid fluid. Fresh sterile hydatid fluid for Casoni's test is sterilised by **Seitz filter**.
- Serodiagnosis: To detect
 - Antibody against **antigen B** (8 and 16 kDa).
 - Antibody against hydatid fluid **fraction 5 antigen**.
- Treatment
 - Early stages: **PAIR** (Puncture; Aspiration; Injection; Reaspiration)
 - Late stages/complicated cyst communicating with biliary tract: **Surgical removal**.

EXTRA EDGE

- Echinococcus multilocularis (alveolaris):** Causes multifocal or alveolar hydatid disease; causes multiple cysts in both lobes of liver; **poor prognosis** and patients can die of liver failure—**mimics liver malignancy**—hence called **malignant hydatid disease**.
- Echinococcus vogeli* and *E. algarthi*: **Polycystic hydatid disease**.

Diphyllobothrium Latum

- A.k.a **Fish** tapeworm; **Longest** tapeworm in man.
- Adults worm is about **10 m** in length with spoon-shaped head with two slit like grooves (bothria).
- Definitive host: Man (optimal host), dogs and cats.
- First intermediate host: **Cyclops**
- Second Intermediate host: Freshwater fish.
- Eggs are **oval, operculated, bile stained** and **NOT infective** to man. (all other cestode eggs are non-operculated!)
- Infective stage: **Plerocercoid** larva.
- Mode of infection: Ingestion of uncooked fish containing **stage 3 plerocercoid larva**.
- Causes **megaloblastic anemia** due to vitamin **B12** deficiency.

Other Tapeworms MCQ Points

- **Hymenolepis nana** is the **MC and smallest tapeworm** in humans.
- **Eggs of H.nana** contains 2 **polar knobs** and 4-8 thread like **polar filaments**.
- **Sparganosis** is the term used for ectopic infection by **sparganums**. (**plerocercoid larva**) of **Spirometra** and some Diphyllobothrium species.

HELMINTHS: TREMATODES (FLUKES)

Classification According to Habitat

Habitat	Trematodes
Blood Flukes (Blood)	Schistosoma hematobium (in vesical/ bladder and pelvic/prostatic venous plexus) Schistosoma mansoni (In Inferior mesenteric vein) Schistosoma japonicum (In superior mesenteric vein)
Liver flukes (Biliary tract)	Fasciola hepatica Clonorchis sinensis Opisthorchis spp.
Respiratory tract (Lung flukes)	Paragonimus westermani
GIT (Small and large intestines—intestinal flukes)	Fasciolopsis buski Heterophyes heterophyes Matgonimus yokogawai Watsonius watsoni Gastrodiscoides hominis

BLOOD FLUKES

Schistosomes

- A.k.a **Bilharziasis** after Theodor Bilharz who first observed the worm.
- **Waterborne** disease affecting Africa, Asia and South America. (In India - in **Ratnagiri district** of Maharashtra)
- Habitat is mentioned in table above.
- Features differentiating Schistosomes from other trematodes are:
 - Schistosomes are **unisexual/dioecious (sexes are separate)**.
 - They produce **non-operculated egg** containing the embryo, **miracidium**.
 - They have **NO redia stage** in larval development
 - There is **NO** second intermediate host.
- Schistosomes have a **leaf-like unsegmented body** with two cup-like **suckers** with delicate spines.
- Intestine is **bifurcated (Y-shaped)**.
- Male is **broader** than female.
- **Definitive host**: Man
- **Intermediate host**: Freshwater **snails**
- **Infective form**: Fork-tailed **cercariae**.
- Diagnosis: Detection of eggs in urine, stool; detection of antigen and antibody.
- **Schistosome eggs** have been mentioned earlier under the topic "Eggs"
- **Praziquantel** is the DOC.

Clinical features of schistosomiasis

- **Swimmer's itch**: Skin rash at site of cercarial penetration (a/w all schistosomes).
- **Katayama fever**: Fever, rash, arthralgia, hepatosplenomegaly due to high worm load (a/w *S.mansoni* and *S.japonicum*)
- Schistosoma **hematobium** specifically causes:
 - **Sandy patches**: Fibrosis of vesical mucosa and formation of egg granulomas.
 - Chronic schistosomiasis: **Bladder stones, bladder calcification** and /w urinary **bladder carcinoma**.
 - Painless **hematuria**
- *S.mansoni* and *S.japonicum*: **Portal hypertension**
- *S.mansoni*: **Peripartal fibrosis (Symmer's or clay pipestem fibrosis)**

EXTRA EDGE

- **Katayama disease** or oriental schistosomiasis refers to disease caused by *S.japonicum*.
- Schistosoma **intercalatum** has **acid-fast eggs**.
- Schistosoma **mekongi** found in **Thailand and Cambodia** along Mekong river.

Fasciola Hepatica and Clonorchis Sinensis

	Fasciola hepatica	Clonorchis sinensis
A.k.a	Sheep Liver Fluke Largest and MC liver fluke	Chinese (Oriental) Liver Fluke
Definitive host	Sheep (also found in biliary tract of man)	Man (also found in biliary tract and pancreatic duct of man)
Intermediate host	Freshwater snails	Snail
Second intermediate host	Aquatic vegetations	Fish
Mode of infection	Ingestion of metacercariae on aquatic plants	Ingestion of metacercariae in infected fish
Clinical	Acute phase: RUQ pain, hepatomegaly. Chronic phase: Biliary obstruction; obstructive jaundice; cholelithiasis, anemia. Halzaun (suffocation) - In Lebanon and North Africa, ingestion of raw liver of infected sheep can cause asphyxia (adult worms attach to pharyngeal mucosa and cause mucosal edema!)	Cholangitis; obstructive jaundice; pigmented gallstones ; biliary cirrhosis and portal HTN; cholangio (bile duct) carcinoma (can also occur with Opisthorchis species).
Treatment	Oral triclabendazole is the DOC ; alternate drug is bithionol	Praziquantel is the DOC

EXTRA EDGE

- Parasites with **water plants** (aquatic vegetation) as the **second intermediate host**: Fasciola hepatica; Fasciolopsis buski; Gastrodiscoides hominis; Watsonius watsoni

INTESTINAL FLUKES

- **Largest trematode** infecting humans: **Fasciolopsis buski** (**giant intestinal fluke**).
- **Smallest trematode** infecting humans: **Heterophyes heterophyes**
- **Gastrodiscoides hominis** is the **ONLY** fluke inhabiting **large intestine** of man. It is **MC in Assam** in India.

LUNG FLUKE: PARAGONIMUS WESTERMANI

- Adult worm is **egg-shaped**, reddish brown and covered with scale like spines.
- Endemic to **Manipur** in India
- Lives in cystic spaces in the lung communicating with bronchi.
- **Definitive host**: Man and domestic animals.
- **Intermediate host**: Snails
- **Second intermediate host**: **Crab or Crayfish**.
- Infective form: Encysted **metacercariae** in crab or crayfish.
- Clinically: **Peribronchial granuloma** and cystic dilatation of bronchi; dyspnea, hemoptysis, bronchiectasis, pneumothorax. Extrapulmonary lesions in brain (**soap-bubble** lesions) and intestine.
- **Praziquantel** is the DOC.

HELMINTHS: NEMATODES

Classification of Nematodes Based on Habitat

Intestinal human nematodes	Somatic human nematodes
<ul style="list-style-type: none"> • Large intestine <ul style="list-style-type: none"> - Trichuris trichura (whipworm) - Enterobius vermicularis (thread or pinworm) • Small intestine <ul style="list-style-type: none"> - Ascaris lumbricoides (roundworm) - Ankylostoma duodenale (Old world hookworm) - Necator Americanus (New world hookworm) - Strongyloides stercoralis - Trichinella spiralis - Capillaria philipensis 	<ul style="list-style-type: none"> • Lymphatics <ul style="list-style-type: none"> - Wuchereria bancrofti - Brugia malayi and timori • Skin/Subcutaneous <ul style="list-style-type: none"> - Loa Loa - Onchocerca volvulus - Mansonella streptocerca - Dracunculus medinensis (guinea worm) • Serous cavity (Peritoneum, Pleura) <ul style="list-style-type: none"> - Mansonella ozzardi and perstans (NON-pathogenic) • Conjunctiva <ul style="list-style-type: none"> - Loa Loa <p>NOTE: In the above list, ALL are Filarial worms except Dracunculus</p>

Nematode Routes of Infection

- Ingested—Enterobius, Ascaris, Trichinella, Trichuris. **"You'll become sick if you EATT these!"**
- Cutaneous—Strongyloides, Ancylostoma, Necator. **"These enter your feet from the SAND".**

Types of female nematodes

- ▶ **Oviparous** (laying eggs)
 - Unsegmented eggs: Ascaris, Trichuris
 - Segmented eggs: Ancylostoma, Necator
 - Eggs containing larvae: Enterobius
- ▶ **Viviparous** (producing larvae): Trichinella, Wuchereria, Brugia, Dracunculus
- ▶ **Ovoviviparous** (laying eggs containing fully formed larvae which hatch out immediately): Strongyloides

Strongyloides Stercoralis

- **Smallest nematode** infecting man.
- Adult worm lives in **duodenum and jejunum**. Female worm is **ovo-viviparous**.
- Egg is **ovoid, thin-walled and transparent**.
- Natural host: Man
- Infective form: **Third stage filariform larva**.
- Mode of transmission: **Penetration of skin by filariform larva** in soil; **autoinfection** can occur.
- Clinical: **Usually benign and symptomatic**; Cutaneous larva migrans (**larva currens**); **bronchopneumonia**; intestinal features (mucus diarrhea, protein losing enteropathy, paralytic ileus).
- **Hyperinfection**: In immunocompromised states (HIV, transplant patients, steroid therapy etc.), numerous adult worms in intestines and lungs and larvae in various tissues and organs may be seen.
- **Diagnosis**:
 - ▶ Demonstration of **rhabditiform larvae** in stool.
 - ▶ **Stool concentration methods** are by (i) Formol ether concentration or (ii) Baermann's funnel gauze.
 - ▶ **Stool culture methods**: Agar plate culture and charcoal culture.
- Larva may also be demonstrated in **sputum, duodenal aspirates** and **jejunal biopsies**.
- Treatment: **DOC is ivermectin or albendazole**.

Trichinella and Trichuris

	Trichinella spiralis	Trichuris trichura (whipworm)
Definitive host	Optimum host: Pig ; Alternate host: Man (dead end host)	Man
Intermediate host	No	No
Infective form	Tightly coiled encysted larvae in the striated muscle of pigs	Embryonated egg containing rhabditiform larva that develops in soil

Contd...

EXTRA EDGE

- **Strongyloides fuelleborni kellyi** causes "**swollen belly syndrome**" in New Guinea in which neonatal infants acquire overwhelming intestinal infection which can also disseminate and maybe fatal in absence of therapy.

Hookworms

	Ankylostoma duodenale	Necator americanus
A.k.a	Old World hookworm	New world hookworm
Size	Larger and thicker	Small and slender
Caudal spine in female	Present	Absent
Eggs/day	15,000–20,000	6000–11000
Development	Faster	Slower
Pulmonary reaction	More common	Less common
Blood loss/worm	0.2 ml/day	0.03 ml/day
Iron loss	0.76 mg/day	0.45 mg/day
Lifespan	2–7 years	4–20 years

- **Natural host**: Man; only single host required.
- Infective form: **Third stage filariform larvae**
- Enters by **penetration of skin**
- Clinical
 - ▶ **Ground itch**: Sever local itching at portal of entry of filariform larva; MC in Necator > Ankylostoma; Self limiting in 2–4 weeks.
 - ▶ **Creeping eruption**: **Cutaneous larva migrans** (more common with animal hookworms)
 - ▶ Respiratory: Bronchitis, bronchopneumonia; rarely Loeffler's syndrome
 - ▶ **Iron deficiency anemia**: Microcytic hypochromic anemia.
- Diagnosis: Stool exam: **Eggs in feces**; Adult worm in **duodenal aspirate**; stool culture by **Harada-Mori method**; **occult blood** and **Charcot Leyden crystals** maybe seen.
- Treatment: Albendazole, mebendazole or pyrantel pamoate.

Contd

	Trichinella spiralis	Trichuris trichura (whipworm)
Clinical	Malaise; periorbital edema ; muscle weakness; myocarditis	Acute appendicitis , abdominal pain, mucus diarrhea, anemia (blood loss of 0.005 ml/worm/day), rectal prolapse
Diagnosis	Muscle biopsy for larvae Bachman's Intradermal test.	Characteristic eggs in stool (Egg is triple shelled ; barrel shaped with mucus plug at each pole. It is bile stained .); Egg counts: Light infection < 10 eggs; Heavy is > 50 eggs per smear; Eosinophilia in early stages
Treatment	Albendazole and mebendazole along with corticosteroids (for severe infection)	Mebendazole or Albendazole.
Extra comments	Small nematode (1.5–3 mm). Female worm is viviparous . Muscles commonly involved: Diaphragm; pectoralis; deltoid; biceps and gastrocnemius. Pathology: Myositis and basophilic degeneration of muscles.	

Enterobius Vermicularis

- A.k.a **pinworm, threadworm or seatworm**.
- Adult worm lives in **cecum and appendix**.
- Eggs are **planoconvex**.
- Natural host: **Man**, single host only.
- Infective form: Embryonated egg containing infective larva.
- Mode of infection: **ingestion** of eggs or **autoinfection**; children and family members are affected.
- Clinical: **Pruritus ani, nocturnal enuresis, appendicitis** (also **salpingitis and peritonitis**).
- Diagnosis: Eggs detection by **NHL swab** and **Scotch tape test**. Detection of adult worm in fingernails or after stool enema.
- Treatment: Albendazole, mebendazole or pyrantel pamoate.

EXTRA EDGE

- **Adult worms** which maybe present in **fecal sample**:
Enterobius
Strongyloides
Taenia solium
H.nana
Entamoeba histolytica
Giardia,
Cryptosporidium parvum
- Nematodes NOT showing **systemic migration** in man: Enterobius and Trichuris.

Ascaris Lumbricoides

- **MC human helminth** that is distributed worldwide.
- **Largest nematode** infection in humans; **cylindrical** worm that lives in small intestine (**85% in jejunum**).

- Natural host: **Man**.
- Infective form: Embryonated egg containing **rhabditiform larva**.
- Clinical:
 - ▶ **Spoiliative (Nutritional)** Action: Protein and vitamin A deficiency.
 - ▶ **Toxic** action: Urticaria and angioedema
 - ▶ **Mechanical** action: Intestinal obstruction, intussusception, volvulus, intestinal perforation
 - ▶ **Lungs**: Pneumonia (Loeffler's syndrome).
- Diagnosis: Eggs in stool or sputum; adult worms in stool.
- Treatment: Albendazole, mebendazole or pyrantel pamoate.

Fertilised ascaris egg

- Always **Bile stained** (golden brown)
- Round or oval
- Contains large **unsegmented ovum**
- Floats in saturated salt solution (**Fertilised Floats!**)

Unfertilised ascaris egg

- Non-bile stained
- Elliptical
- Contains **small atrophied ovum** with refractile granules
- Does NOT Float (it is the heaviest of all helminthic eggs!)

EXTRA EDGE

- **Toxocara canis** (in dogs) and **Toxocara cati** (in cats) are also roundworms.
- **T.canis** is the **MC cause** of **visceral larva migrans**.
- **Bayliascaris** is present in raccoons in North America and can cause cutaneous and visceral larva migrans; also **neural larva migrans**.

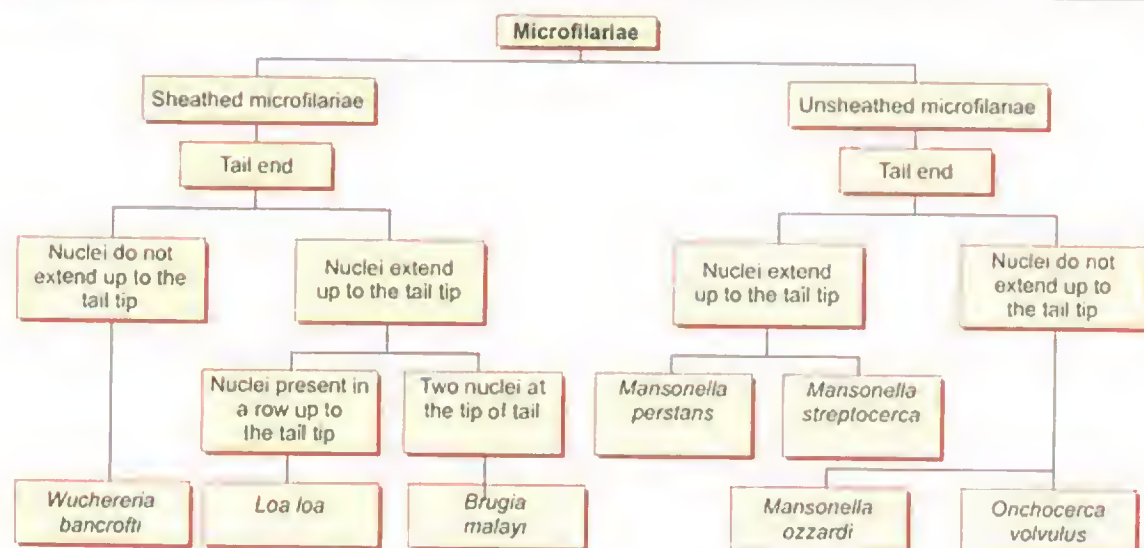
FILARIAL WORMS

Introduction: Key Points

- All Filarial worms also belong to *Nematodes*.
- Classification of filarial worms has been **mentioned earlier** in the table titled "Classification of Nematodes based on habitat".
- M.ozzardi* and *M.perstans* are **non-pathogenic**.
- Female worm is **viviparous** and give birth to larvae called microfilariae.

- Microfilarie* maybe further classified based on whether they are (i) **sheathed or unsheathed** AND on (ii) characteristic **arrangement of nuclei**. (See **flowchart 6.1**).
- Filarial life cycle has two hosts: **Definitive host (man)** and **Intermediate host** (blood sucking **arthropods vectors**).
- Adult filarial worm contains an **endosymbiotic Rickettsia-like alpha-propiono-bacterium** of the genus **Wolbachia** spp.—this has become a **new target for antifilarial chemotherapy**.

Flowchart 6.1: Differentiating features of various microfilariae on the basis of presence of nuclei in tail end



Different types of periodicity exhibited by microfilariae

- Nocturnal periodicity:** When the largest number of microfilariae occur in blood at night, e.g. *Wuchereria bancrofti*
- Diurnal periodicity:** When the largest number of microfilariae occur in blood during day, e.g. *Loa loa*
- Nonperiodic:** When the microfilariae circulate at constant levels during the day and night, e.g. *Onchocerca volvulus*
- Subperiodic or nocturnally subperiodic:** When the microfilariae can be detected in the blood throughout the day but are detected in higher numbers during the late afternoon or at night.

Note: The microfilariae are found in capillaries and blood vessels of lungs during the period when they are not present in the peripheral blood.

Filarial Nematodes and their Vectors

Parasite	Vector
Lymphatic filariasis	
<i>Wuchereria bancrofti</i>	<i>Culex quinquefasciatus</i>
<i>Brugia malayi</i>	<i>Mansonia</i> spp.
<i>Brugia timori</i>	<i>Anopheles barbirostris</i>
Conjunctival filariasis	
<i>Loa Loa</i>	<i>Chrysops</i> spp.
Subcutaneous filariasis	
<i>Onchocerca volvulus</i>	<i>Simulium</i> spp.
<i>Mansonella streptocerca</i>	<i>Culicoides</i>
Serous cavity filariasis	
<i>M.ozzardi</i> and <i>perstans</i>	<i>Culicoides</i>

Clinical Features of Filariasis

- The term "**Filaris**" is traditionally only applied to lymphatic disease caused by either *Wuchereria* or *Brugia* (and NOT to all other filarial worm diseases).
- Clinical features, lab diagnosis and treatment are **same** in both types.
- Pathogenic effect in Wucheriasis is due to adult (living/dead). Living microfilariae in blood are NOT known to produce any pathogenic effect.

	Classical filariasis	Occult filariasis
Cause	Due to adult and developing worm	Hypersensitivity to microfilarial antigen
Basic lesion	Lymphangitis, lymphadenitis	Eosinophilic granuloma formation
Organs involved	Lymphatic vessels and lymph node	Lymphatic system, liver, lung, spleen, joints
Microfilariae	Present in blood	Present in tissues BUT NOT in blood
Serological tests	CFT not so sensitive	CFT highly sensitive
Response to Diethyl Carbamazine (DEC)	NO response	Prompt response

Classical Filariasis

- Acute adenolymphangitis; lymphangitis; lymphadenitis; lymphedema; lymphangioma.
- Hydrocele
- Lymphorrhagia (rupture of lymphatic varices leading to chylous urine, chylous ascites, chylothorax)
- Elephantiasis** (obstructive lymphedema)

Occult Filariasis (Myers Kouwenaar syndrome)

- Massive **eosinophilia**
- Hepatomegaly
- Features of classical filariasis are **absent**.
- Tropical pulmonary eosinophilia** (Weingarten's syndrome)
 - Low grade fever, loss of weight

Key Points of Other Filariae

Parasites	Features
<i>Onchocerca volvulus</i>	<ul style="list-style-type: none"> Transmitted by female blackflies (<i>Simulium</i>) Ocular: "river blindness"; sclerosing keratitis, secondary glaucoma, chorioretinitis, optic atrophy

- Dry cough, dyspnea, wheezing.
- Eosinophilia (>50,000)

Lab Diagnosis of Filariasis

- Detection of microfilaria**
 - By thick and thin blood smear stained with Giemsa stain. Night blood sampled between **10 PM–4 AM** are taken.
 - Blood concentration techniques are used when microfilarial density is low
 - Knott's concentration technique
 - Nucleopore filtration
 - DEC provocative test (small dose of DEC can cause microfilariae to appear in the blood even during daytime)
- Ultrasound + Doppler: Motile adult worm maybe seen ('filaria dance' sign)
- Demonstration of circulating antigen
 - Trop-Bio** test
 - IgG4 antibody against *W.bancrofti* antigen **WbSXP-1**
 - Immunochromatographic test is a rapid test that detects *W.bancrofti* antigen by using **monoclonal antibody-12**.

Treatment of Filariasis

- DEC (Diethylcarbamazine)** is the **DOC**.
- Dose:** 6 mg/kg body weight for 12 days amounting to total of 72 mg/kg body weight.
- DEC medicated salt:** At a dose of 1-4 mg/kg of salt has been used for filariasis control in **Lakshadweep**.

EXTRA EDGE

- Favourite site for *W.bancrofti* is **Globus major** of epididymis.
- Malayan** filariasis is characterised by **absence of chyluria** and **rarity of scrotal swelling**.
- Brugia pahangi** is a parasite of dogs and cats in **Malaysia** and can infect man and can lodge in the right heart (hence called '**heartworm**') and pulmonary artery. The dead worm becomes an embolus and causes pulmonary infarcts—can appear as a '**coin lesion**' on chest X-ray and be mistaken for malignancy.

Contd.

Parasites	Features
	<ul style="list-style-type: none">Subcutaneous nodules (onchocercoma)Lizard skin: Lymph nodes or portions of bowel may hang in the skinLeopard skin: Hypopigmented patches in AfricansSowdah: Hyperpigmented patches in ArabicsTreatment: Ivermectin for DOC ("IVERmectin for rIVER blindness")
Dracunculus Medinensis (Guinea worm)	<ul style="list-style-type: none">Guinea worm has been eradicated in India.Definitive host: Man; Intermediate host: CyclopsInfective form: Cyclops containing stage 3 larvae.Clinical: Pruritus, rash, subcutaneous blister, cellulitis.Diagnosis: Detection of worm in the ulcer.Treatment: Ancient method of removing the worm by twisting around a stick is effective; or else surgical removal.
Loa Loa	<ul style="list-style-type: none">Transmitted by mango fly (Chrysops) - day biting flies.Swelling in skin: Calabar swellings or 'fugitive swelling'Ocular: Can see worm <i>crawling in conjunctiva</i>; granuloma; <i>painless edema of eyelids and proptosis</i>DOC: Diethylcarbamazine (DEC).

PROTOZOA

Introduction

- Single celled (**unicellular**) **eukaryotic** micro-organisms belonging to **kingdom protista** are classified as Protozoa.
- This single cell performs **all** the functions: reproduction, digestion, respiration, excretion etc.
- Karyosome** is a DNA containing body situated peripherally or centrally within the nucleus (E.histolytica; E.coli).
- Chromatoid body**: Refers to extranuclear chromatin material (as in E.histolytica cyst)
- Non-nuclear DNA present in addition to the nucleus is called **kinetoplast**.
- Trophozoites** are active feeding and growing stage of protozoa.
- Cysts** are resting or resistant stage of protozoa bounded by tough cell wall.
- Life cycle:
 - Protozoa like intestinal flagellates and ciliates require **only 1 host** and are transferred to another host in the **cyst form**.
 - In some protozoa like **Plasmodium**—Sexual reproduction occurs in one host (man) and asexual reproduction occurs in another host (mosquito).

Reproduction in protozoa

- Maybe asexual or sexual.
- Asexual reproduction
 - Binary fission
 - Longitudinal binary fission: Flagellates
 - Transverse binary fission: Ciliates
 - Multiple fission (**schizogony**): Plasmodium
- Sexual reproduction
 - **Conjugation**: Balantidium coli
 - **Gametogony (syngamy)**: Sporozoa, plasmodium.

Classification of Amoebae

- Free living amoebae**: All are opportunistic pathogens
 - **Naegleria fowleri** (brain eating amoeba!) is free living amoeba that causes **primary amoebic meningo-encephalitis**; rapidly **fatal**; acquired by swimming in **fresh water lakes**. Cysts enter from nose via cribriform plate.
 - **Acanthameba** spp. causes **keratitis** (described in ophthalmology chapter (Pg 550)) and **granulomatous amebic encephalitis** (especially in immunocompromised).
 - Balamuthia mandrillaris
- Intestinal amoebae**:
 - All intestinal amoebae (E.coli, E.hartmani, E.nana, E.gingivalis are commensals) are non-pathogenic **except** E.histolytica.

Entamoeba Histolytica

- It occurs in 3 forms: Trophozoite, precyst and cyst.
- Trophozoite** shows typical ameboid movement is crawling or gliding motility. It divides by **binary fission**.
- Precystic stage**: Contains large **glycogen vacuole** and **2 chromatid bars**.
- Cystic stage**: Contains a **mass of glycogen, 1-4 chromatoid bodies** and 4 nuclei. Thus the **mature cyst is quadrinucleate**.
- The glycogen mass appears **golden brown** with iodine staining and with iron hematoxylin stain the glycogen is unstained.
- Host: **Only Man**.
- Infective form: **Mature quadrinucleate cyst** in feces.
- Mode of infection: By swallowing food/water contaminated with cysts.
- Incubation period: **4 days-4 months**.
- Clinically

- Intestinal amoebiasis: **Flask shaped** intestinal ulcers; granulomatous growth called **ameboma** (MC in **cecum/rectosigmoid junction**); amoebic **dysentery** (*fever absent; patient non-toxic; stool does not stick to container*).
- Extra-intestinal: **Amoebic Liver Abscess (anchovy sauce pus)**; can also involve lungs, skin and genital system.
- Diagnosis:
 - Stool exam for cysts or dead trophozoites; **Charcot Leyden crystals** maybe seen.
 - Stool culture: More sensitive; Media include Boeck's; NIH; Craigs; Nelsons; Robinsons and Balamuth media.
- Treatment:
 - BOTH tissue and luminal amebicides: **metronidazole; tinidazole**.
 - Tissue amebicides: Chloroquine
 - Luminal amebicides: Diloxanide furoate/ iodoquinol

Summary of Important Protozoa

Protozoa and transmission	Clinical features	Diagnosis	Treatment
Giardia intestinalis (lamblia)	VSSPs (Variant Surface Specific Proteins) play a role in virulence	Trophozoites (falling leaf motility) or cysts in stool; ' String test/ enterotest for duodenal contents obsolete; ELISA for Giardia antigen in feces	Metronidazole is the DOC
Ingestion of cysts in water and food	Causes Giardiasis: bloating flatulence foul-smelling non-bloody diarrhea (often seen in campers/hikers)		
Trichomonas vaginalis	Vaginitis : Foul-smelling frothy greenish discharge , itching and burning; strawberry cervix	Trophozoites (motile) on wet mount ; Gold standard for diagnosis is culture of vaginal secretions	Metronidazole is the DOC (treat both partners)
Sexually transmitted; Trophozoite itself is infective since NO cyst form			
Trypanosoma cruzi ,	South American Trypanosomiasis or Chagas disease (<i>dilated cardiomyopathy, megacolon, mega-esophagus</i>);	Blood smear for trypto-mastigotes ; Culture on NNN medium (Novy, McNeal, Nicole)	Nifurtimox and benznidazole have been used but no specific effective treatment
Recluid bug bite transmits trypto mastigotes	Romana's sign : Swelling near eye where bite has occurred		
Trypanosoma brucei gambiense (West African) and rhodesiense (East African)	African trypanosomiasis (sleeping sickness) ; Stage 1 - hematogenous and lymphatic dissemination; Stage 2 - CNS involved;	Blood smear or wet mount of lymph node aspirate; Culture in Weinman or Tobie's medium; ELISA, PCR	Stage 1: Pentamidine is DOC for gambiense and Suramin is DOC for rhodesiense; Stage 2 with CNS involved: Melarsoprol is the DOC
Tsetse fly bite transmits trypto mastigotes	Winterbottom's sign : Posterior cervical lymphadenopathy		
Babesia	Babesiosis fever and hemolytic anemia; jaundice.	Blood smear for intraerythrocytic parasite ; reticulocytosis; hemoglobinuria	Atovaquone + azithromycin (OR clindamycin + quinine)
Booby tick bite			

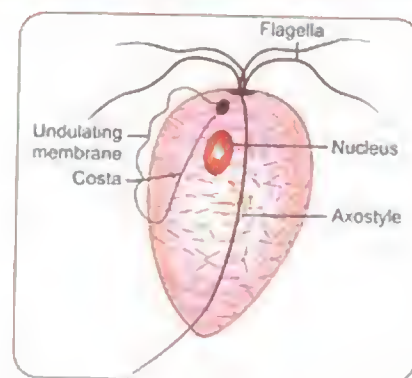
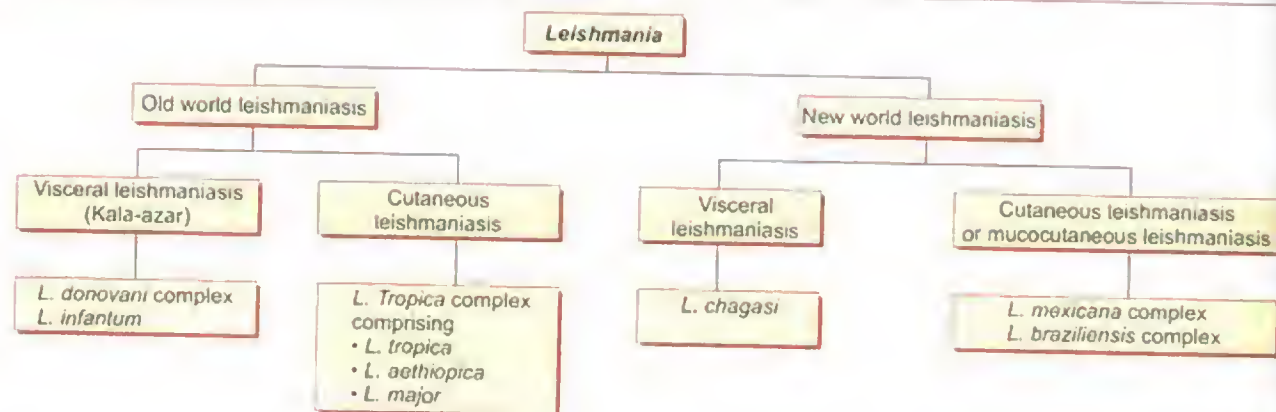


Fig. 6.8: T. vaginalis

Leishmaniasis

Flowchart 6.2: Distribution and disease caused by Leishmania spp.



Old World Leishmaniasis (Leishmania donovani)

- All members of genus Leishmania are **obligate intracellular parasites** that pass their life cycle in 2 hosts
 - Definitive Host: Man (contain amastigote form)
 - Vector: **Female Sandfly (Phlebotomus)** contain **promastigote** form.
- Mode of transmission: Bite of infected sandfly transmits promastigotes.
- Visceral Leishmaniasis (Kala Azar)**
 - Affects **reticulo-endothelial** system
 - Splenomegaly** (MC affected organ); hepatomegaly; lymphadenopathy; bone marrow infiltration; anemia, leukopenia, thrombocytopenia; Skin is dry, dark and **hyperpigmented** (hence Kala Azar); cachexia and emaciation.
- Post-kala-azar dermal leishmaniasis (PKDL)**
 - PKDL is a sequelae of visceral leishmaniasis that appears 1-2 years after patients have been cured of visceral leishmaniasis in endemic areas.
 - PKDL is prevalent in all areas where Leishmania donovani is endemic (**East Africa** especially Sudan,

and on the Indian subcontinent, especially in **Bihar and Bangladesh**).

- PKDL can appear as (i) **hypopigmented macules** on face and trunk resembling tuberculoid leprosy (ii) erythematous patches in butterfly distribution and (iii) nodules on the face.
- Diagnosis:
 - Demonstration of **LD bodies** in thick blood films
 - Culture in NNN medium to demonstrate promastigotes
 - Nonspecific serum tests are **Napier's aldehyde test** and **Chopra's antimony test** which give indirect evidence
 - Skin test: **Montenegro** or Leishmanin skin test.
 - Detection of antibody using **rk 39** antigen or **WKA antigen**.
- Treatment:
 - Pentavalent antimonial** compounds are the **DOC** in endemic areas: **Sodium stibogluconate** or **meglumine antimoniate** (IV or IM)
 - BUT** in India (**Bihar**) resistance is present and hence **Amphotericin B** is the **DOC**

- For **PKDL**, **oral miltefosine** > amphotericin B is the **DOC**.

EXTRA EDGE

- Miltefosine** is the **first oral drug** approve for Leishmaniasis.
- Leishmaniasis is also covered under **Dermatology** chapter (Pg 1077)

Toxoplasma Gondii

- Definitive host: Cat; Intermediate host: Man
- Mode of infection: Ingestion of food containing **oocyst** and **tissue cyst**.
- Clinical toxoplasmosis maybe congenital or acquired
 - Congenital toxoplasmosis**
 - Transmitted transplacentally from **mother to fetus**.
 - Chorioretinitis, Cerebral calcifications; Convulsions; deafness, mental retardation, microcephaly, hydrocephalus.
 - Acquired toxoplasmosis**: Usually asymptomatic; can cause **posterior cervical lymphadenopathy** (MC).
 - Ocular toxoplasmosis**: Uveitis, chorioiditis ('**head-light in fog**' appearance), chorioretinitis, panuveitis.
 - In AIDS/Immunocompromised: **CNS colonisation - ring enhancing lesions on MRI**.
- Diagnosis: **Serology** is the **mainstay of diagnosis**; ELISA for antigen and antibody detection.
- Treatment: **Sulfadiazine + pyrimethamine + folinic acid**. For prophylaxis in **HIV** patients, **trimethoprim-sulfamethoxazole** is the **DOC**.

PLASMODIUM AND MALARIA

History of Plasmodium

- Alphonse Laveran**, a French army surgeon in Algeria first discovered Plasmodium in RBCs of a patient.
- Ronald Ross** in Secunderbad, established the mode of transmission of malaria by identifying the developing stages of plasmodium in mosquitoes.
- Both Ross (1902) and Laveran (1907) won Nobel Prizes.

Distribution of Malaria

- P. vivax**: **Most common** and **most widely distributed** in the world.
- P. falciparum**: **Predominant species in Africa** and is **rapidly spreading** in Asia and India.
- P. malariae**: Rare except in Africa
- P. ovale**: **Rarest (in the world and India)**; Confined to West Africa

- P. knowlesi**: Endemic in **south east Asia** (Malaysia, Borneo), BUT is **absent in Africa**.
- In India,
 - P. falciparum** and **P. vivax** are the MC species causing malaria, their proportion being around **50% each**.
 - P. vivax** is **more prevalent in the plain areas**
 - P. falciparum** predominates in **forested and hilly areas**.
 - P. malariae** has been reported in Orissa
 - P. ovale** is extremely rare.
- Mnemonic: "**Virat Century, O (zero) Rare**" = **VCOR** = "**Vivax Commonest Ovale Rarest**"!

WHO Endemicity Classification

Endemicity	Parasite rate and spleen rate	Indicates
Hypoendemic	< 10%	Transmission is low
Mesoendemic	11-50%	Transmission is moderate
Hyperendemic	51-75%	Transmission is intense BUT seasonal
Holoendemic	> 75%	Transmission of high intensity

EXTRA EDGE

- Parasite rate**: % of children between 2-10 years showing malarial parasite in their blood films
- Spleen rate**: % of children between 2-10 years showing enlargement of spleen.

Plasmodium knowlesi

- A.k.a. the "**fifth**" malarial parasite.
- Primarily a **zoonosis**—natural host is the **primate Mocoque monkey**.
- Endemic in South east Asia** (Malaysia, Borneo, Philippines, Myanmar); but is **ABSENT** in Africa.
- Transmitted by bite of **Anopheles** mosquito.
- Affects **adults** mainly.
- Asexual cycle of parasite in humans is **24 hours**—hence called "**quotidian**" malaria.
- Malaria is **non-relapsing**.
- Treatment: Chloroquine and Primaquine.

Host and Vector

- Definitive host**: Female anopheles mosquito (sexual phase occurs)
- Intermediate host**: Man (asexual phase occurs)
- Vector**: Female Anopheles mosquito
- Life cycle is shown in below figure

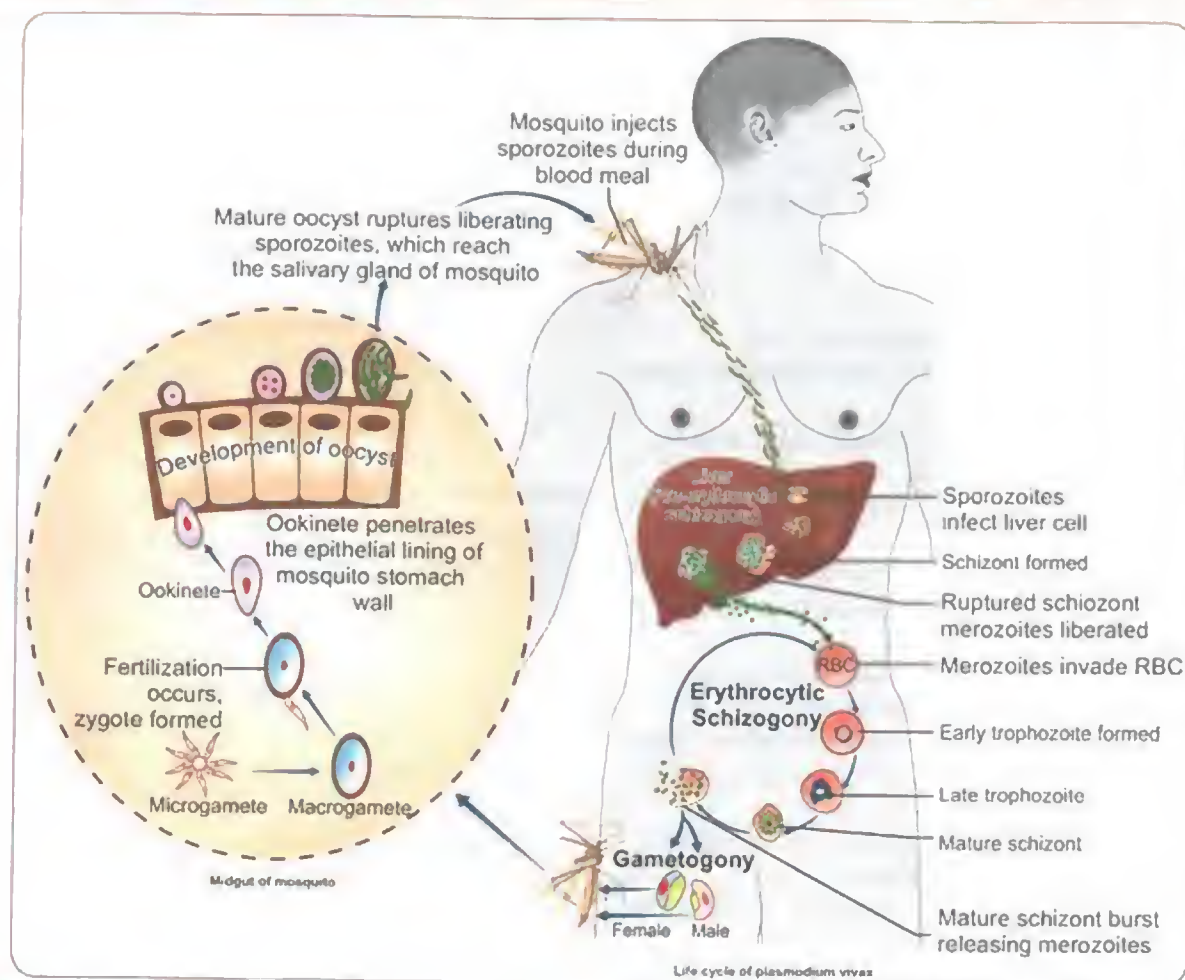


Fig. 6.9: Life cycle of the Plasmodium vivax

Life Cycle of Plasmodium

• Pre-erythrocytic schizogony:

- Development of sporozoites in liver parenchyma
- Liberated merozoites are called as 'Cryptozoites'
- NO clinical manifestation, no pathological change
- Blood is sterile

• Erythrocytic schizogony:

- Parasite resides **inside RBCs**; passes through stages of Trophozoite, Schizont, merozoite
- Parasitic multiplication brings clinical attack of malaria

• Gametogony:

- Some merozoites develop in RBCs of spleen and bone marrow to form 'Gametocytes'

• Exo-erythrocytic schizogony:

- Persistent of late tissue phase in liver

- Seen in *P.vivax* and *P.ovale*

- Cause relapse in Vivax and Ovale malaria

- Liberated merozoites are known as 'Phanerozoites'

• Mosquito cycle of plasmodium

- Completion of gametogony:
- Exflagellation of microgamete and maturation of gametes
- Fusion of gametes form 'Zygote'; zygote matures to 'Ookinete'

• Sporogony:

- Ookinite develops into 'Oocyst'
- On 10th day of infection, oocyst ruptures, releasing sporozoites; sporozoites reach salivary glands
- Mosquito at this stage is capable of transmitting infection.

Differential Diagnosis of Plasmodia

	Disease course	RBC preference	Infected RBC shows
<i>P. falciparum</i>	Tertian (fever occurs after 48 h)	Reticulocytes, normal and mature RBCs (all types)	Banana shaped gametocyte; Highest parasite burden; Mature ring trophozoites show Maurer's clefts , Double chromatin dots (headphones appearance!), Accole forms . Multiple infection (>1 parasite invades RBCs).
<i>P. vivax</i>	Tertian, benign	Reticulocytes (young RBCs)	Schuffner's dots present;
<i>P. malariae</i>	Tertian, benign	Reticulocytes (young RBCs)	Pear shaped fimbriated RBCs, James dots
<i>P. ovale</i>	Quartan (fever occurs after 72 h), benign	Mature RBCs	Ziemann's dots

EXTRA EDGE

- **Latent Liver hypnozoites** are present only in *P. ovale* and *P. vivax* —leads to long-term **relapses in ovale and vivax** malaria. ("With **Ovale** and **Vivax**, it's never **OVER!!**")
- Please NOTE: *P. malariae* and also *P. falciparum* causes **recrudescence** and NOT a true relapse; the differences between relapse and recrudescence are mentioned in below table

Recrudescence and Relapse

Recrudescence	Relapse
Seen in <i>P. falciparum</i> ; <i>P. malariae</i>	Seen in <i>P. ovale</i> , <i>P. vivax</i>
Due to persistence of parasite at a subclinical level in blood circulation	Due to reactivation of latent hypnozoites in liver cells
Occurs within few week-months of previous attack	Occurs 24 weeks - 5 years after previous attack
Can be prevented by drug therapy or use of newer antimalarial drugs in case of drug resistance	Can be prevented by giving primaquine to eradicate hypnozoites

Clinical Features of Malaria

- **Fever with rigors; anemia, splenomegaly** (early with *P. vivax* and *P. falciparum*, late in *P. malariae*).
- Complications:
 - *P. falciparum* = Malignant tertian malaria; **Cerebral malaria**, **Blackwater fever** (DIC and renal failure); **Algid malaria** (peripheral circulatory failure)

- *P. vivax* = splenic rupture. "**Whyvax** (vivax) spleen?!"
- *P. malariae* = Nephrotic syndrome. "**Malariae** is Nepharious".

Microorganism	Microbial ligand	Host receptor
Plasmodium Vivax	Merozoite form	Duffy Fy antigen
Plasmodium falciparum	Erythrocyte binding protein (EBA 175)	Glycophorin A

EXTRA EDGE

- Histopathology of Liver in malaria shows: **Kupffer cell hyperplasia** with **periportal infiltration** by pigment laden macrophages (Robbins Pg 392).
- **Durck granuloma**: Seen in brain in **cerebral malaria**.

Merozoite-induced Malaria

- Natural malaria is sporozoite induced (infection being transmitted through sporozoites introduced by bite of mosquitoes). Injection of merozoites can lead to direct infection of red cells and erythrocytic schizogony with clinical disease. Such merozoite-induced malaria may occur in the below situations
- 1. **Blood Transfusion malaria**: Parasite may remain viable in stored blood for 1-2 weeks; Pre-erythrocytic schizogony and hypnozoites are absent; relapse does NOT occur and incubation period is short; Infective stage is the **trophozoite** (verified from various textbooks and journals).
- 2. **Congenital malaria**
- 3. **Renal transplantation**
- 4. **Shared syringes** between drug addicts.

Innate Immunity against malaria

- ▶ **Duffy negative** RBCs - are protected from *P. vivax* infection.
- ▶ Hemoglobin:
 - **HbE** protects against *P. vivax* infection
 - **HbS** protects against *P. falciparum*
 - **HbF** protects against all *Plasmodium* species
- ▶ **G-6-PD deficiency** protects against malaria
- ▶ **HLA B53** protects against cerebral malaria
- ▶ Nutrition: **Iron deficiency and severe malnutrition** are relatively resistant to malaria
- ▶ Pregnancy and splenectomy **increase susceptibility** to malaria

Lab Diagnosis of Malaria

- Demonstration of plasmodia in **thin and thick blood smear** and examination by Leishman, Giemsa or JSB stain.
- **Immunofluorescence** staining and Quantitative Buffy Coat (QBC) smear.
- Fluorescence microscopy: **Kawamoto** technique
- Rapid immunochromatographic test for detecting malaria antigen (**Pf-ITRP-2** and **pLDH**). Examples: Parasite F test and Dual antigen test.
- Molecular tests: PCR and DNA probes.

EXTRA EDGE

- **Malaria Vaccines:** Vaccine against *Plasmodium falciparum*, technically named **RTS, S/AS01 (also called Mosquirix)** will be administered to children between ages of 5-17 months in 3 African nations Kenya, Ghana and Malawi in 2018. It targets the **pre-erythrocytic** stage.
- **Roll-back malaria** launched jointly by WHO, UNICEF, UNDP and World Bank in 1998.
- World **Malaria day - April 25th** of every year.
- **"Malaria Month"** in India: **June** every year.

Parasitology Clinical Hints

Findings	Organism
Brain cysts, seizures	<i>Taenia solium</i> (cysticercosis)
Liver cysts	<i>Echinococcus granulosus</i>
B12 deficiency	<i>Diphyllobothrium latum</i>
Biliary tract disease	<i>Clonorchis sinensis</i>
Hemoptysis	<i>Paragonimus westermani</i>
Portal hypertension	<i>Schistosoma mansoni</i>
Hematuria, bladder cancer	<i>Schistosoma haematobium</i>
Microcytic anemia	<i>Ancylostoma</i> , <i>Necator</i>
Perianal pruritus	<i>Enterobius</i>

MORE HIGH YIELD POINTS

- **Morular Mott cells** are seen in histopathology of brain in African Trypanosomiasis. (Mott cells are also seen in multiple myeloma)—Mott cell is a plasma cell with multiple eosinophilic inclusion composed of immunoglobulins.
- Piperazine causes **flaccid paralysis** of worms.

More One-Liners

- Largest protozoa - *Balantidium coli*
- Smallest intestinal amoeba - *Dientamoeba fragilis*
- Smallest tapeworm found in human intestine - *H. nana*
- Largest helminth (largest worm) - *T. saginata* (beef tapeworm)
- Largest liver fluke - *F. hepatica*
- Largest trematode infecting man - *Fasciolopsis buski*
- Largest Nematode - *Ascaris*
- Smallest Nematode - *Trichinella*
- Only protozoan parasite found in small intestine of man - *Giardia lamblia*
- Only ciliate protozoan parasite of man - *Balantidium coli*
- Parthenogenic worm (female is able to produce fertile eggs or larvae without fertilization) - *Strongyloides stercoralis*

CHAPTER

7

AIDS

HIV Chronology

- **1981:** AIDS was first recognized in the USA when the US Center for Disease Control and Prevention (CDC) reported the unexplained occurrence of *Pneumocystis carinii* pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma in 26 previously healthy homosexual men in New York and Los Angeles.
- **1983:** HIV was isolated from a patient with lymphadenopathy by **Luc Montagnier**
- **1984:** First case of AIDS in the South-East Asia Region (SEAR) of World Health Organization was reported from Thailand
- **1985:** ELISA for HIV was developed
- **1986:** HIV/AIDS was first found in India among commercial sex workers of Chennai.
- **2009:** **Luc Montagnier** was awarded the Nobel prize for discovery of HIV.

About Human Immunodeficiency Virus (HIV)

- ▶ Family: **Retroviridae**
- ▶ Subfamily: **Lentivirinae**
- ▶ Genus: **Lentivirus**
- ▶ **Transforming** retroviruses: Human T-cell
- ▶ **Lymphotropic** Viruses (HTLV) I and HTLV-II.
- ▶ **Cytopathic** retroviruses: Human Immunodeficiency Viruses, HIV-1 and HIV-2.

Viral Structure

- HIV is a single-stranded RNA (ss-RNA) retrovirus.
- HIV virion is an **icosahedral** structure
- Size of HIV viral particle is about **120-150 nm**.
- **gp 120:** External envelope proteins; "**spike**" antigen
- **gp 41:** Transmembrane envelope proteins
- **p24:** Rectangular core/capsid protein
- **p18:** Nucleocapsid protein

- **HIV genome** has 3 major sections
 - ▶ **gag** region: encodes **viral core** proteins (including p24).
 - ▶ **pol** region: encodes **viral enzymes** [reverse transcriptase (p51), protease (p10) and integrase (p32)]
 - ▶ **env** region: encodes **viral envelope** proteins (gp120 and gp41)
- The major difference between the genomes of HIV-1 and HIV-2 is the fact that **HIV-2 lacks the vpr gene** and has a **vpx gene** not contained in HIV-1.

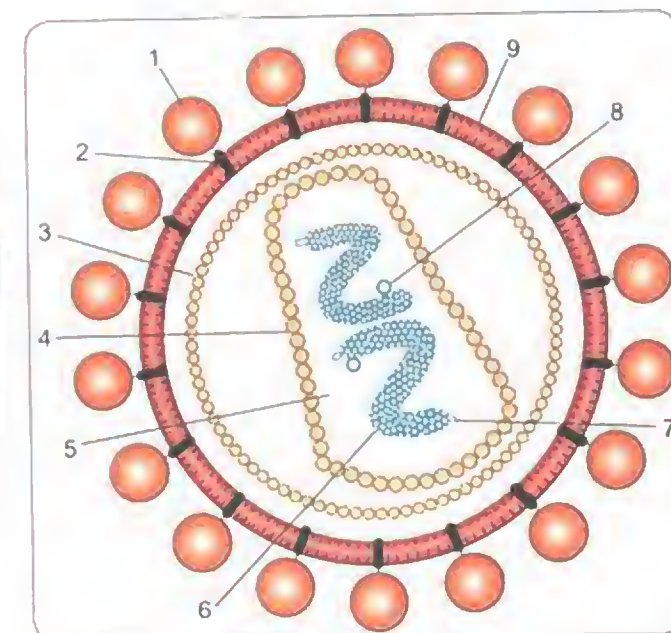
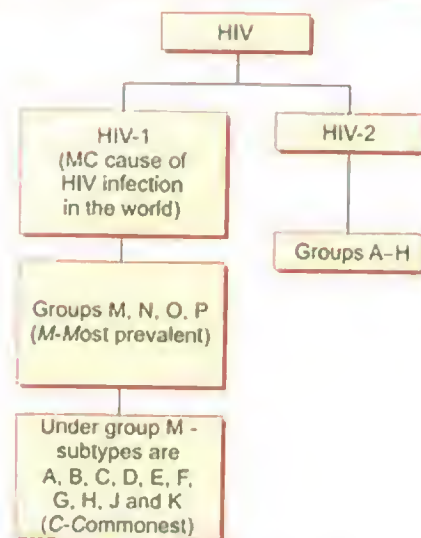


Fig. 7.1: Structure of HIV (diagrammatic representation)
 1. Envelope glycoprotein spike (gp120), 2. Transmembrane pedicle glycoprotein (gp41), 3. Outer icosahedral shell of nucleocapsid (p18), 4. Cone shaped core of nucleocapsid (p24), 5. Inner core, 6. Viral proteins associated with RNA, 7. Viral RNA, 8. Reverse transcriptase, 9. Envelope lipid bilayer



- **HIV-1 is MC cause of HIV disease** throughout the world.
- **HIV-1, Group M, subtype C** is **most prevalent** (responsible for most infections)
 - In the world
 - Also in India (except in the North-East India where subtype E may predominate) and in
 - Sub-Saharan Africa (2/3 of HIV/AIDS infected people live here).
- **HIV 1, Group M, subtype B** is more common in—USA and Western Europe.

Transmission

- | | |
|---------------------------------|--|
| Sexual | <ul style="list-style-type: none"> • MC method of transmission is heterosexual contact (both in India and the world) • Male to female transmission is more efficient • Also transmitted by homosexual contact • unprotected receptive anal intercourse has highest risk of transmission in both sexes. |
| Blood and blood products | <ul style="list-style-type: none"> • "Most Efficient" method of transmission (risk of transmission is >90%). • HIV-tainted blood transfusions blood products, tissue transplantation, IV drug abusers • Risk of transmission by needlestick prick is 0.3% (1:300) and after mucus membrane exposure is 0.09%. |
| Maternal-fetal/Infant | <ul style="list-style-type: none"> • During pregnancy, during delivery (highest risk) or during breastfeeding. • Antiretroviral therapy of mother from the beginning of II trimester to 6 weeks post delivery combined with Cesarean section significantly protects fetus/infant from infection. |
| By other body fluids | <ul style="list-style-type: none"> • Although theoretically possible, there is NO EVIDENCE that HIV transmission can occur as a result of exposure to saliva, sweat, tears and urine. |

Pathogenesis

- After entry into the cell, the viral **reverse transcriptase** enzyme (hence retrovirus) makes a **DNA copy of the RNA genome**, which integrates into the host cell DNA. **Viral replication then occurs** producing complete virions, which are released from the infected cell by **characteristic budding**. The number of circulating viruses (viral load) predicts progression to AIDS.
- The dissemination of virus to lymphoid organs in particular, is a major factor in the establishment of a chronic and persistent infection.
- The **two major co-receptors for HIV-1** are **CCR5** and **CXCR4**. (Note: **Maraviroc** is effective only against CCR5 positive viruses and two assays—**Trofile assay** and **Phenoscript assay** are used to find if the patient's virus is susceptible to maraviroc).
- **Dendritic cells (DCs)** may play an important role in the initiation of HIV infection by virtue of the ability of HIV to bind to **cell-surface C-type lectin receptors**, particularly **DC-SIGN** (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin)—encoded by **CD209**.

CD4+ T Lymphocytes

- The hallmark of HIV disease is a **profound immunodeficiency** resulting primarily from a **progressive quantitative and qualitative deficiency of the subset of T lymphocytes** referred to as **CD4+ helper-inducer T lymphocytes—the primary cellular receptor for HIV**.
- CD4+ cells are destroyed by **apoptosis**.
- The CD4+ T cell count is the lab test generally accepted as the **best indicator of the immediate state of immunologic competence** of the patients with HIV infection.
- HIV also binds to **CD4 receptors** on **monocytes, macrophages and neural cells**.

Stages of HIV Infection

- **Acute infection:** often asymptomatic.
- **Seroconversion:** May be accompanied by a transient illness: fever, malaise, myalgia, pharyngitis, maculopapular rash or meningoencephalitis (rare).
- **Persistent generalized lymphadenopathy (PGL):** defined as nodes >1 cm diameter at 2 extra-inguinal sites, persisting for 3 months or longer.
- **AIDS-related complex (ARC):** **prodrome of AIDS**; non-specific constitutional symptoms (fever, night sweats, diarrhea, and weight loss) AND minor opportunistic infections, e.g. **oral Candida, oral hairy leukoplakia, herpes zoster, recurrent herpes simplex, seborrheic dermatitis, tinea infections**.

- **Full Blown Acquired immune deficiency syndrome (AIDS):** An HIV infected individual with a CD4+ T cell count of less than 200/ml. has AIDS by definition regardless of the presence of symptoms or opportunistic disease.
- **AIDS-dementia complex**
- The **median time** from primary HIV infection to the development of AIDS in untreated individuals is approximately **10 years**.

Lab Diagnosis of HIV Infection

ELISA

Screening test for HIV infection. **Sensitivity >99.5%**; to avoid false positive results, positive results should be confirmed with Western blot

Western blot

MC Confirmatory test for HIV. Specificity when combined with ELISA -99.9%. Imprecise results occur with early HIV infection, HIV 2 infection, autoimmune disease, pregnancy and recent tetanus toxoid administration.

HIV rapid antibody test

Screening test for HIV; Sensitivity and specificity is 99%; produces results in **10–20 minutes**; requires little training to perform test; positive results must be confirmed with standard test (Western Blot)

Absolute CD4 lymphocyte count

Most widely used predictor **for HIV progression**

CD4 lymphocyte percentage

Percentage may be **more reliable than the CD4 count**; Risk of progression to an AIDS opportunistic infection or malignancy is high with percentage < **14%** in the absence of treatment.

HIV viral load tests

These tests measure the **amount of actively replicating HIV virus**. Correlate with disease progression and response to antiretroviral drugs.

Tests for Direct Detection of HIV

Immune complex—dissociated p24 antigen capture assay

Measurement of levels of **HIV-1 core protein** in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment; **Indicates active HIV replication**. Tends to be **positive prior to seroconversion (window period)** and with advanced disease; useful in **acute HIV syndrome**

HIV RNA by PCR

PCR amplification of cDNA generated from viral RNA (target amplification)

Contd...

HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification
HIV RNA by TMA	Target amplification of HIV-1 RNA via reverse transcription followed by T7 RNA polymerase
HIV RNA by NASBA	Isothermic nucleic acid amplification with internal controls

Key: bDNA, Branched DNA; cDNA; Complementary DNA; EIA, Enzyme immunoassay; NASBA, Nucleic acid sequence based amplification; PCR, Polymerase chain reaction; TMA, Transcription mediated amplification.

Prophylaxis-Based on CD4 Counts

CD4 count	Risk	Drug of choice
< 200 /μL	<i>Pneumocystis pneumonia</i>	TMP-SMX , 1 DS tablet daily; Alternatives include <i>dapsone plus pyrimethamine plus leucovorin</i> ; <i>aerosolized pentamidine</i> administered by nebulizer; and <i>atovaquone</i>
< 100/μL	<i>Toxoplasmosis</i>	TMP-SMX , 1 DS tablet daily; Alternatives include <i>dapsone plus pyrimethamine plus leucovorin</i> ; and <i>atovaquone</i>
< 50/μL	<i>CMV retinitis</i>	Valganciclovir 900 mg twice daily or ganciclovir sustained release implant every 6 monthly
< 50/μL	<i>Mycobacterium Avium Complex (MAC)</i>	Azithromycin (1200 mg weekly) or Clarithromycin (500 mg BD); Alternative is rifabutin 300 mg/day

TMP-SMX: Trimethoprim-sulfamethoxazole

Prophylaxis against Mycobacterium Tuberculosis

- **Indications:**
 - Skin test >5 mm
 - Positive IFN-gamma release assay
 - Prior positive test without treatment
 - Close contact with case of active pulmonary TB.
- **DOC: Isoniazid** 300 mg + **Pyridoxine** 50 mg qd x 9 months or Isoniazid 900 mg twice weekly + Pyridoxine 50 mg PO daily x 9 months
- **If Isoniazid resistant: Rifabutin** 300 mg or **Rifampin** 600 mg PO qd x 4 months.

Contd...

CDC Stage 3 (AIDS)—Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

EXTRA EDGE

- The 3 AIDS defining malignancies are:
 - Kaposi sarcoma
 - B cell NHL (primary cerebral lymphoma)
 - Invasive cervical cancer.

RESPIRATORY DISEASE

Most commons in AIDS respiratory system

- **MC opportunistic infection** a/w AIDS: **P.**
- **MC** manifestation of pulmonary disease: **pneumonia**.
- **MC** cause of pneumonia in AIDS: **P.jirovecii** infection.
- **MC atypical** mycobacterial infection in AIDS: **M.avium** or **M. intracellulare** – **M. ovium** complex (**MAC**).
- For MAC infection: ↑ risk with CD4+ T cell count < 50/μL
- **S.pneumoniae** is **MC** cause of community acquired **bacterial pneumonia** in AIDS.
- Worldwide **1/3 of AIDS deaths** are a/w **TB**.
- HIV infection ↑ risk of developing active TB by a factor of **100**.
- **Acute bronchitis** and **sinusitis** are prevalent in all stages of HIV infection.
- Two forms of idiopathic interstitial pneumonia in HIV infection: lymphoid interstitial pneumonitis (**LIP**) and nonspecific interstitial pneumonitis (**NIP**).
- **About LIP**
 - **MC** in children (> 1 year), benign self-limiting asymptomatic condition,
 - LIP is characterized by **nodule formation and diffuse infiltration of the alveolar septae by lymphocytes, plasma cells and immunoblasts**.
 - There is **NO** involvement of blood vessels and **NO** destruction of lung tissue.

PNEUMOCYSTIS

Clinical

- Formerly known as *Pneumocystis carinii* pneumonia (**PCP**); ↑ risk with CD4+ T cell count < 200/μL.
- Fever, cough (usually **nonproductive** or with scanty white sputum); shortness of breath; **burning retrosternal chest pain**; **honeycomb exudates** within alveolar spaces.
- CXR:
 - Diffuse faint bilateral interstitial infiltrate or perihilar infiltrates are most characteristic (seen in only two-thirds of patients).
 - Normal CXR seen in 5–10% of patients
 - Apical cavity in patients who have received aerosolized pentamidine

Diagnosis

- Hypoxemia with ↓ in PaO₂; ↑ in arterial-alveolar (a – A) gradient; **definitive diagnosis** is by **demonstration of**

trophozoite or cyst form of the organisms in samples obtained from induced sputum, bronchoalveolar lavage, transbronchial biopsy or open lung biopsy (**methenamine silver** staining).

- Elevated serum LDH in 95% (low specificity); serum beta-glucan test is more sensitive and specific

Extrapulmonary Features

- One polypoid mass (in primary infection);
- In patients receiving aerosolized pentamidine for PCP prophylaxis (ophthalmic lesions of choroids, necrotizing vasculitis resembling Buerger's disease, bone marrow hypoplasia, intestinal obstruction).

Treatment and Prophylaxis

- **Treatment:**
DOC is **Trimethoprim/Sulfamethoxazole (TMP/SMZ)**
Alternative treatments are **dapsone/ trimethoprim**, and **clindamycin/primaquine**;
Intavenous pentamidine in severe disease in patients unable to tolerate TMP/SMZ.
For patients with a PaO₂ < 70 mm Hg or with an (a – A) gradient > 35 mm Hg, adjunct **glucocorticoid therapy** should be used with antimicrobials.
- **Prophylaxis:**
DOC is **TMP/SMZ**, one double-strength tablet daily.
Alternatives include **dapsone plus pyrimethamine plus leucovorin**; aerosolized pentamidine administered by nebulizer; and **atovaquone**.

CARDIOVASCULAR DISEASE

- **MC heart disease** is **coronary artery disease**.
- **HIV associated Cardiomyopathy** (late complication) – **dilated cardiomyopathy** a/w congestive heart failure (CHF).
- Pericardial effusion, Cardiac tamponade, Pulmonary arterial HTN may occur.

GIT DISEASE

- **Oral lesions** common in patients with untreated HIV infection include **oral candidiasis (thrush)**, **oral hairy leukoplakia**—NOT premalignant (caused by EBV), and **aphthous ulcers**.
- **Cryptosporidia**, **Isospora belli**, and **microsporidia** are common opportunistic protozoa causing diarrhea in HIV infected patients.
- Over 90% of HIV positive patients have evidence of **coinfection with HBV**.
- In AIDS, **pancreatic injury** is **MC** secondary to **drug toxicity** (pentamidine or dideoxynucleotides).

Renal disease

- **HIVAN—HIV associated nephropathy**;
- **Early** manifestation seen more in Africans and Hispanics, also in children;
- **Proteinuria** is hallmark;
- **Edema and hypertension** are rare;
- Diagnosis is by renal biopsy—shows **focal segmental glomerulosclerosis**.
- Treat with antiretrovirals, ACE inhibitors and prednisolone.

CNS DISEASE

- **Toxoplasmosis**
 - It is the **MC intracerebral space-occupying lesion** in HIV-infected patients;
 - Contrast MRI/CT shows—multiple contrast-enhancing lesions on CT scan with a predilection for the basal ganglia—**ring enhancement** a/w an eccentric nodular area of enhancement: **eccentric target sign**.
- **HAND = HIV-Associated Neurocognitive Disorders**; **Frascatti criteria** is used for clinical staging of HAND.
- **HIV associated dementia** (AIDS dementia complex)—late feature of HIV infection; virus gains CNS access via infected macrophages; **first sign may be deterioration in handwriting**.
- **Progressive multifocal leukoencephalopathy (PML)** due to **JC virus**
- **Cryptococcus neoformans** is the **MC cause of meningitis** in patients with AIDS. Cryptococcal meningitis presents with fever and headache and a positive latex agglutination test that detects cryptococcal antigen.
- **Primary CNS Non-Hodgkin's lymphoma**, solitary, usually + for EBV, late feature of AIDS with CD4 < 50.
- The **MC peripheral neuropathy** in HIV infection is a **distal sensory polyneuropathy**.

SKIN DISEASES

- **Seborrheic dermatitis** is **MC skin disease** in HIV;
- Others: Reactivation herpes zoster (shingles), eosinophilic pustular folliculitis, Kaposi's sarcoma; **bacillary angiomatosis** (*Bartonella henselae* and *quintana*)

KAPOSI'S SARCOMA (KS)

- KS is a **multicentric neoplasm** consisting of **multiple vascular** nodules appearing in the skin, mucus membranes and viscera. **Human Herpes Virus-8 (HHV-8)** has been strongly implicated as a viral co-factor in the pathogenesis of KS.

- Lesions occur in **sun exposed** areas and in areas of trauma (**Koehner phenomenon**).
- **Pulmonary KS**: CXR shows **bilateral lower lobe infiltrates** that obscure the margins of the mediastinum and diaphragm
- **Fewer than 10%** of AIDS patients with KS die as a consequence of their malignancy and death from **secondary infections** is considerably more common.

OTHER DISEASES

- HAART therapy may cause **lipodystrophy** consisting of elevations in **plasma triglycerides, total cholesterol and apolipoprotein B, hyperinsulinemia and hyperglycemia**.
- **Generalized wasting** is an AIDS-defining condition; defined as **involuntary weight loss of >10%** a/w **intermittent or constant fever and chronic diarrhea or fatigue lasting >30 days** in the absence of a defined cause other than HIV infection.
- The incidence of **cervical dysplasia** in HIV-infected women is 40%.
- Three main categories of lymphoma seen in HIV infection: **Grade III or IV immunoblastic lymphoma (MC—60%)**, Burkitt's lymphoma, and **primary CNS lymphoma** (commonly **a/w EBVQ**): Approximately 90% of these lymphomas are **B cell in phenotype**.

Immune reconstitution inflammatory syndrome (IRIS)

- **Paradoxical worsening** of clinical condition is seen following the **initiation of antiretroviral therapy**
- Occurs weeks to months following the initiation of antiretroviral therapy
- Is most common in patients starting therapy with a **CD4+ T cell count under 50/L** who experience a precipitous drop in viral load
- Is frequently seen in the setting of tuberculosis. **Can be fatal**.

OCULAR MANIFESTATIONS OF AIDS

- **Cotton-wool spots** are the **MC ocular lesions** seen in 70% of patients with AIDS. These are **asymptomatic and disappear spontaneously** after several weeks. Possible causes include immune complex deposition and HIV infection of vascular endothelium.
- **Retinal microangiopathy**: MC retinopathy in AIDS;
- **Anterior segment complications**:
 - Eyelid: Blepharitis, Molluscum contagiosum, Kaposi's sarcoma (eyelid or conjunctival); Herpes Zoster Ophthalmicus (**HZO**).

- Conjunctival Kaposi sarcoma, squamous cell carcinoma and microangiopathy.
- Keratitis due to herpes simplex, Microsporidial and herpes zoster.
- Keratoconjunctivitis sicca
- **Anterior uveitis** (usually secondary to systemic drug toxicity: **rifabutin and cidofovir**).
- Other fundus lesions: Pneumocystis carinii chorioretinitis, toxoplasma retinitis, progressive outer retinal necrosis (**PORN, caused by varicella zoster virus**), toxoplasmosis atypical, cryptococcus chorioiditis, and B cell intraocular lymphoma.

Immune reconstitution inflammatory syndrome (IRIS)

- **Cytomegalovirus retinitis** is the **MC opportunist eye infection** and the **MC cause of visual loss in AIDS patients**. Its appearance usually signifies severe systemic involvement
- Vasculitis and exudation: "**Pizzo-pie, Cottage cheese and tomato ketchup, mozzarella cheese appearance**".
- "**Brushfire like extension**" along vessels: "**frosted branch angiitis**"
- Treatment includes
 - Intravitreal: **Intravitreal ganciclovir implant (Vitrasert)**, fomivirsen, cidofovir.
 - Prophylaxis for CMV retinitis is started when CD4 count < 50 cells/mm³ and stopped when CD4 count is > 100–150 cells/mm³.

POST-EXPOSURE PROPHYLAXIS, PEP (NACO)

- As per **revised NACO guidelines**, drugs used for post-exposure prophylaxis are **Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600 mg)** once daily for **28 days**.
- **Single pill** containing this formulation should be used. **Dual drug regimen should NOT be used any longer** in any situation for PEP.
- The first dose of PEP should be administered as soon as possible (preferably **within 2 hours of exposure**) and the subsequent dose should be given at **bed time** with clear instruction to take it **2–3 hours after dinner and to avoid fatty food in dinner**.
- In case of intolerance to efavirenz, regimen containing Tenofovir + Lamivudine + **PI** (protease inhibitor) can be used.

HIV IN CHILDREN

Primary route of infection in children is **vertical transmission**, i.e. from mother to child. HIV may be transmitted from mother to child by:

Intrapartum (during delivery)—MC method of transmission (15%)

- During breastfeeding. (risk 0.5% per month)
- Transplacentally (during pregnancy in utero)

Diagnosis of HIV in Children

In children < 18 months

- Because of the persistence of the maternal IgG HIV antibody, infants younger than 18 months require virologic assays that **directly detect HIV** in order to diagnose HIV infection.
- Preferred virologic assay is **HIVbDNA PCR**; HIV RNA assays are more difficult.

In children > 18 months

- **Anti HIV IgG antibody** detection by **ELISA and Western Blot** is used.

As per NACO guidelines:

- In child < 6 months born to HIV positive mother:
 - Collect and Send **Dried Blood Spot (DBS)** of babies between **6 weeks to <6 months** of age for **HIV-I DNA PCR**
 - Rapid antibody test NOT recommended
 - If baby is < 6 weeks HIV-I DNA PCR test **not** recommended
 - 6 weeks and above is the **optimal age** for routine first HIV-I DNA PCR test
 - Establish **definitive diagnosis at 18 months** by HIV antibody test
- In children 6–18 months born to HIV positive mother
 - Collect blood and test for HIV antibodies using rapid test. Also prepare a dried blood spot for HIV-I DNA PCR.

Reducing PPTCT or Reducing MTCT

- PPTCT = Prevention of Parent to Child Transmission
- MTCT = Mother to Child Transmission

Care of Mother

- All pregnant and breastfeeding women living **with HIV** receive **lifelong triple-drug ART regimen** regardless of CD4 count or WHO clinical stage

ANTIRETROVIRAL DRUGS (ANTI-HIV AGENTS)

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**
 - **Drugs**: Abacavir Didanosine Emtricitabine Lamivudine, Stavudine, Tenofovir Zalcitabine, Zidovudine,
 - **Mechanism**: NRTIs inhibit the reverse transcriptase enzyme; prevent incorporation of viral genome into host DNA.
- **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)**
 - **Drugs**: Etravirine, Delavirdine, Efavirenz, Nevirapine, Rilpivirine
 - **Mechanism**: NNRTIs inhibit the reverse transcriptase enzyme; prevent incorporation of viral genome into host DNA

- The recommended **first-line regimen** for HIV infected pregnant women is **Tenofovir (TDF) (300 mg) + Lamivudine (3TC) (300 mg) + Efavirenz (EFV) (600 mg)** at any gestational age.
- Safe delivery techniques
 - Do NOT rupture membranes artificially (keep membranes intact for as long as possible)
 - The membranes should be left intact as long as possible and artificial rupture of membrane reserved for cases of foetal distress or delay in progress of labour.
 - Minimize vaginal examination and use aseptic techniques
 - Avoid invasive procedures like foetal blood sampling, foetal scalp electrodes.
 - Avoid instrumental delivery as much as possible
 - Avoid routine episiotomy
 - Suctioning of infant with nasogastric tube should be avoided unless there is meconium staining of the liquor.

EXTRA EDGE

- As per **NACO guidelines Coesoreon section** is NOT recommended for prevention of mother-to-child-transmission and is done only if there is an **obstetric indication** for the same. (particularly since women are taking anti-retroviral therapy for their own health and have taken adequate duration of prophylaxis for PPTCT).

Care of HIV exposed infant

- **Exclusive breastfeeding for 6 months** (It is NOT a contraindication these days with anti-retroviral prophylaxis being given to child. It is also necessary to prevent malnutrition).
- **NO mixed feeding** (No mixing of breastfeeding and other alternate feeding like milk powder/cow's milk during the first 6 months) under any circumstances.
- **Syrup Nevirapine** (10 mg in 1 ml. suspension) from birth **till 6 weeks or till 12 weeks** (in cases where mother is diagnosed with HIV during labor or immediately postpartum and is planning to breastfeed)
- From **6 weeks to 18 months Cotrimoxazole Prophylaxis** for opportunistic infections.

Contd...

- **Protease Inhibitors (PIs)**
 - **Drugs:** Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Tipranavir, Lopinavir, Fosamprenavir, Darunavir, Atazanavir.
 - **Mechanism:** Inhibit assembly of new virus by blocking protease in progeny virions.
- **Entry Inhibitors—Fusion Inhibitors**
 - **Drug:** *Enfuvirtide*
 - **Mechanism:** Bind viral *gp41 subunit*; inhibit conformational change required for fusion with CD4 cells, therefore block entry and subsequent replication.
 - **Clinical use:** IN patients with persistent viral replication in spite of antiretroviral therapy; used in combination with other drugs
- **Entry Inhibitors—CCR5 antagonists**
 - **Drug:** *Maraviroc*
 - **Mechanism:** Specifically, maraviroc blocks the chemokine receptor CCR5 which HIV uses as a coreceptor to bind and enter a human helper T cell.
- **Integrase Inhibitors**
 - **Drug:** *Raltegravir, dolutegravir*
 - **Mechanism:** Raltegravir inhibits Integrase, and prevents the integration of viral genetic material into human chromosomes—also called *strand transfer inhibitors*; the drug is metabolized away via *glucuronidation*.

ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):** NRTIs are associated with **lactic acidosis, hepatic steatosis, and body fat redistribution (lipodystrophy)**. Most drugs need dose adjustment for renal failure.
- **Zidovudine** *Anemia (macrocytic), neutropenia, skeletal and cardiomyopathy, bone marrow suppression, lactic acidosis, headache, GID, hyperpigmentation of skin and nails, insomnia*
Used for prevention of maternal fetal HIV transmission. Twice-daily dosing preferred over thrice-daily dosing. Fatigue, nausea, headache, and myalgia usually resolve 2–4 weeks after initiation.
- **Zalcitabine** *PN, pancreatitis, oral ulcers*
- **Didanosine** *Pancreatitis, dry mouth, hepatitis, PN, GID, hyperuricemia, renal failure, rash, seizures, ? increased MI*
Concomitant alcohol use may increase risk of pancreatitis.
- **Lamivudine** *Headache, rash, dry mouth, abdominal pain, pancreatitis, PN rare*
Active against HBV; Lamivudine is **best tolerated** and **least toxic** of the NRTIs
- **Stavudine** *PN, pancreatitis, dyslipidemia, diarrhea, hepatitis, neutropenia*
Of the NRTIs, stavudine has greatest risk of **lipodystrophy** and other mitochondrial toxicity.
- **Emtricitabine** *Hyperpigmentation of palms and soles; Headache, nausea, insomnia*
Active against HBV
- **Abacavir** *Hypersensitivity syndrome* (in HLA B5701+ patients, can be fatal), rash, headache, GID
Risk of hypersensitivity related to certain genetic factors, particularly HLA B5701
- **Tenofovir** *Acute and chronic renal insufficiency, Renal osteomalacia, Fanconi syndrome*
Active against HBV
Gastrointestinal symptoms may be worse in lactose-intolerant patients; tenofovir is formulated with lactose.
- **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs):** NNRTIs are a/w **rash**, and may cause Stevens-Johnson syndrome and toxic epidermal necrolysis. All NNRTIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

- **Delavirdine** *Rash, Fatigue, ↑ LFTs, hepatitis, GID*
100 mg tablets can be dissolved in water. Seldom used; less potent than other NNRTIs.
- **Efavirenz** *CNS symptoms*— abnormal dreams, drowsiness, confusion; ↑ in LFTs, hyperlipidemia, **QTc prolongation** (torsade des pointes)
Teratogenic in animal studies; contraindicated during pregnancy
- **Nevirapine** *Rash, ↑ LFTs, hepatitis, liver failure*
Hepatotoxicity may be life threatening. It is more common at higher CD4 cell counts, in women, and in patients with hepatitis B or C.
- **Etravirine** *Rash*
- **Rilpivirine** *Depression, rash*
- **Protease Inhibitors (PI):** All PIs are associated with metabolic abnormalities including **dyslipidemia, hyperglycemia, insulin resistance, and body fat redistribution (lipodystrophy)**. (Atazanavir is less likely to cause dyslipidemia.) PIs may increase the risk of bleeding in hemophiliacs; PIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required. All PIs are potent inhibitors of CYP3A4. (saquinavir is least potent)
- **Saquinavir** *GID, ↑ LFTs, headache, oral ulcerations*
Must be used in combination with low-dose ritonavir.
- **Ritonavir** *GID, ↑ LFTs, fatigue, perioral parasthesia, taste perversion, hyperuricemia, hypertriglyceridemia*
Potent P-450 inhibitor; avoid combining oral solution with metronidazole or disulfiram—may cause disulfiram-like reaction.
- **Indinavir** *Nephrolithiasis, flank pain, indirect hyperbilirubinemia, ↑ LFTs, alopecia, dry skin, ingrown nails, insomnia, taste distortion*
To reduce risk of nephrolithiasis, patients should drink at least 1.5 liters of fluid daily. *Rifampicin* reduces blood conc. of indinavir.
- **Amprenavir** *Diarrhea, GID, ↑ LFTs, rash, perioral parasthesia*
May cause rash in patients sensitive to or intolerant of sulfonamides. The oral solution should not be combined with metronidazole or disulfiram; it contains propylene glycol and may cause disulfiram-like reaction.
- **Atazanavir** *Hyperbilirubinemia, jaundice, ↑ LFTs, PR interval prolongation*
Proton pump inhibitors and other antacid medications and H2 blockers interfere with atazanavir absorption and are contraindicated/should be used with caution for use by patients receiving atazanavir.
- **Fosamprenavir** *GID, ↑ LFTs, rash*
Prodrug of amprenavir. May cause rash in patients sensitive to or intolerant of sulfonamides.
- **Lopinavir/ritonavir** *GID, dyslipidemia, ↑ LFTs, taste perversion, perioral parasthesia*
Oral solution contains 42% alcohol. Avoid combining oral solution with metronidazole or disulfiram—cause disulfiram-like reaction.
- **Tipranavir** *Intracranial hemorrhage, GID, ↑ LFTs, rash,*
Must be coadministered with ritonavir; should never be used without ritonavir boosting.
- **Darunavir** *Rash, hepatotoxicity, IRIS (immune reconstitution inflammatory syndrome)*
Always used in **combination with ritonavir**
- **Nelfinavir** *Hepatotoxicity, hyperglycemia, IRIS*
Sweetener **aspartame** used in nelfinavir contains **phenylalanine**.
- **Cobicistat** *Jaundice* (especially when used with *atazanavir*); *Drug interactions* leading to renal failure with some other drugs.
It is a **pharmacokinetic enhancer**; these are used in HIV treatment to increase the effectiveness of an HIV medicine included in an HIV regimen. Used in combination with darunavir or atazanavir

• Entry Inhibitors

• Enfuvirtide (Fusion Inhibitor)	<i>Injection site reactions:</i> erythema, cysts, and nodules at injection sites; neutropenia, ↑ frequency of bacterial pneumonia	Requires extensive patient counseling on injection technique, adherence, and management of possible side effects.
• Maraviroc (CCR5 coreceptor antagonist)	GID, ↑ LFTs, hepatitis, <i>nasopharyngitis</i> , fatigue, dizziness, headache, joint pain, muscle pain	Many drug-drug interactions; dose adjustment needed with many other antiretrovirals and/or other medications.

• Integrase Inhibitors

• Raltegravir	<i>Rhabdomyolysis</i> (↑ <i>creatinine kinase</i>), GID, ↑ in amylase and LFTs, headache, dizziness, abnormal dream, pruritis, <i>rash</i> , fatigue, muscle pain	
• Dolutegravir	GI upset	
• Elvitegravir	Headache, insomnia	

Key: GID: Gastrointestinal distress. PN: Peripheral neuropathy. LFT: Liver function tests, CNS: Central nervous system.

PSM POINTS ABOUT HIV

- The **adult HIV prevalence in India is estimated to be 0.27%** translating into 2.1 million people living with HIV/AIDS in 2011.
- India has **third highest burden of HIV** in the world.
- On the other hand, **India is highest Tuberculosis (TB) burden country** in the world.
- **High HIV prevalence states** (Group I): Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur and Nagaland; here HIV infection has crossed **5% mark in high risk group and 1% or more in antenatal women**.
- **Injecting drug use** is the **MC cause of HIV epidemic in north eastern states** of India.
- "**Avahan**" program is a combined prevention approach for people at high risk for contracting **AIDS**.
- HIV is easily **killed by heat**; it is readily inactivated by *ether, acetone, ethanol (20%), and beta-propiolactone* (1:400 dilution); it is relatively resistant to ionizing radiation and UV light.
- To date **only blood and semen** have been **conclusively shown** to spread the virus.
- **TB is the MC infection among HIV infected people in India.**
- HIV is the most powerful risk factor for the progression of TB infection to TB disease. This is substantiated by the fact that **an HIV-positive TB infected person has a 50-60% lifetime risk of developing TB disease** compared to an HIV-negative TB infected person who has a 10% lifetime risk of developing TB disease.
- **Sub-Saharan Africa** is the region most affected by AIDS pandemic.
- On 1st December 2003, WHO and UNAIDS announced a detailed plan to reach the "**3 by 5 target**" of providing antiretroviral treatment to 3 million people by the year 2005.
- AIDS has earlier been called "**slim disease**".
- Only live vaccine given in HIV patients is MMR.
- **Condoms** are the **best choice for contraception in HIV positive patients** because they prevent HIV transmission during intercourse; *nonoxynol-9* (although a spermicide) is **contraindicated**.
- **IUCDs** are NOT recommended for HIV positive women.

"MOST COMMONS" IN AIDS

Most common	Comments
MC opportunistic infection	TB in India and the world also
MC pulmonary disease	Pneumonia
MC space occupying lesion	Toxoplasmosis (Primary CNS lymphoma is 2 nd MC)
MC hematologic abnormality in HIV	Anemia
MC HIV drugs causing Myopathy	Zidovudine

Contd...

Most common	Comments
MC skin disease	Seborrheic dermatitis
MC endocrinologic abnormality in HIV-infected men	Hypogonadism
MC malignancy	Kaposi's sarcoma
MC electrolyte abnormality	Hyponatremia, SIADH
MC presentation of syphilis in HIV	condyloma lata, a form of secondary syphilis
MC fungal infection (overall)	Candidiasis
MC systemic fungal infection	Cryptococcosis
MC Lymphoma	(NHL): B cell immunoblastic lymphoma (CNS lymphoma)
MC heart disease	Coronary heart disease
MC route of mother to child transmission of HIV	Perinatal/intrapartum (during delivery)
MC cause of pancreatitis in HIV	Drug toxicity
MC ocular lesions	Cotton wool spots
MC cause of blindness	CMV retinitis

Immunology

- Immune system of the body is lymphoreticular system.
- Lymphoreticular system is a complex organization of cells of diverse morphology distributed widely in different organs and tissues of the body responsible for the immunity.

Lymphoreticular System Components

- **Lymphoid system:** It includes lymphoid organs and following cells:
 - T-cells and B-cells
 - Null cells (Large granular lymphocytes): NK cells, LAK cells, antibody dependent cytotoxic cells (ADCC).
 - Lymphoid (plasmacytoid) dendritic cells.
- **Reticular system:** It includes-
 - Phagocytes: Macrophages, microphages (neutrophils, eosinophils)
 - Reticular system: Interstitial (follicular) dendritic cells, Langerhans dendritic cells.

Lymphoid Organs

- The lymphoid system consist of all of the tissue aggregates and organs composed of lymphoid tissue which function together to produce specific resistance to immunity.
- The lymphoid organs are divided into:

Primary (central) lymphoid organ	Secondary (peripheral) lymphoid organ
The sites where cells of lymphoid system are produced In these organs, precursor lymphocytes proliferate, develop and acquire immunological capability Examples are: • Thymus • Bone marrow	The sites where the cells of lymphoid system function After maturity, lymphocytes accumulate in these organs Examples are: • Lymph nodes • Spleen • Mucosa associated lymphoid tissue (MALT) • Lymphoid tissue in gut, lungs, liver and bone marrow

EXTRA EDGE

- **Bone marrow** acts as *central* as well as *peripheral* lymphoid organ.
- **Spleen** is the **largest** lymphoid organ.
- **Thymus** is the *first organ* to become predominantly lymphoid

Definitions

- **Antigen:** Any substance which, when introduced parenterally into the body **stimulates the production of an antibody** with which it reacts specifically and in an observable manner.
- **Complete antigen:** Able to induce antibody formation and produce a specific and preservable reaction with the antibody so produced.
- **Haptens:** These are substances *incapable of inducing antibody formation by themselves*, but can react specifically with antibodies.
 - **Complex haptens** can precipitate with specific antibodies.
 - **Simple haptens** are nonprecipitating.
- **Epitope:** **Smallest unit of antigenicity** is known as **antigenic determinant or epitope**.
- **Premunition:** Immunity to reinfection lasts only as long as the original infection remains active. Once the disease is cured, the patient becomes susceptible to the organism again, e.g. seen in syphilis.
- **Ag-Ab complex:** Is held together by weaker intermolecular forces such as *Van Der Waal's forces, Hydrogen bonds, ionic bonds*, rather than by the firmer covalent bonding.
- **Antibody:** B cell-produced molecules consisting of immunoglobulin heavy and light chains; antibody can exist as B cell-surface antigen-recognition molecules or as secreted molecules in plasma and other body fluids.
- **Dendritic cells:** Myeloid and/or lymphoid lineage **antigen-presenting cells** of the **adaptive immune system**. Dendritic cells are key initiators both of innate immune responses via cytokine production and of adaptive immune responses via presentation of antigen to T lymphocytes.

• **Innate immune system:** Ancient immune recognition system of host cells bearing germline-encoded pattern recognition receptors that recognize pathogens and trigger a variety of mechanisms of pathogen elimination.

➤ Cells of the innate immune system include natural killer (NK) cell lymphocytes, monocytes/macrophages, dendritic cells, neutrophils, basophils, eosinophils, tissue mast cells, and epithelial cells.

• **Pattern recognition receptors (PRRs):** Germline-encoded receptors expressed by cells of the *innate immune system* that recognize PAMPs.

• **Pathogen-associated molecular patterns (PAMPs):** Invariant molecular structures expressed by large groups of microorganisms that are recognized by host cellular pattern recognition receptors in the mediation of *innate immunity*.

• **Plasmacytoid cells** are a newer subset of dendritic cells - pDCs - which are antigen presenting cells.

• **DC-SIGN:** (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) - encoded by **CD209; cell-surface C-type lectin receptors** important in pathogenesis of HIV infection.

• **Natural Killer (NK) Cells**

➤ There are large granular lymphocytes that recognise antigens on target, e.g. on tumour cells, and lyse targets. Important in **resistance to virus infection and malignancy**.

➤ They play a role in **antibody-dependent cytotoxicity**

➤ Identified by: Fc receptor for IgG

Lymphocytes

B lymphocytes	T lymphocytes
<ul style="list-style-type: none"> • Bone marrow-derived or <i>bursal-equivalent</i> lymphocytes • Humoral immunity; make antibody (Ig); control of pyogenic bacteria; prevention of blood borne infections; neutralization of toxins • Produced in germinol centers of lymph nodes and spleen • Constitutes 12% of total lymphocytes • Responsible for hypersensitivity types 1,2,3 	<ul style="list-style-type: none"> • Thymus-derived lymphocytes • Cell mediated immunity; protection against intracellular organisms protozoa and fungi; graft rejection; control of neoplasms • Produced in paracortical regions of lymph nodes and spleen • Constitutes 75% of total lymphocytes • Responsible for cell mediated hypersensitivity (type 4)

Distinguishing Features of T-Cell and B-Cell

Property	T-cell	B-cell
Surface immunoglobulins	-	+
Receptor for Fc piece of IgG	-	+
EAC rosette (C3 receptor)	-	+
SRBC rosette	+	-
Thymus specific antigens	+	-
Blast transformation with PHA	+	-
Concanavalin A	+	-
Endotoxins	-	+
Numerous microvilli on surface	-	+
Phagocytic action	-	-

Cytotoxic T cells

- Cytotoxic T cells have **CD8** which only recognize antigens in association with **HLA class I** molecules on the surface of a cell.
- They kill virus infected, neoplastic and donor graft cells by apoptosis.
- Release cytotoxic granules: **Perforin; granzyme and granulysin**.

Helper T cells

- Have **CD4** which recognize antigens on macrophages and B cells (antigen presenting cells) in association with **HLA-D, class 2** antigens.

Th1 cell	Th2 cell
Regulates cell mediated response	Regulates humoral response
Secretes Th1: cytokines IL2, IFN-γ	Secretes Th2 cytokines: IL4, IL5, IL6
Inhibited by IL10	Inhibited by IFN γ

Types of Immunity

- **Active immunity:** Induced **after exposure to foreign antigens**; slow onset; long lasting protection (memory); e.g. natural infections including subclinical infection, vaccines, toxoid
- **Passive Immunity:** Based on **receiving preformed antibodies from another host**; rapid onset; short lifespan of antibodies (half life = 3 weeks), e.g. IgA in breast milk, antitoxin, humanized monoclonal antibody; immunoglobulin injections.
- **Adaptive Immunity:** effected by **transfer of immunocompetent cells** shares the features of active and passive immunity.

Major Components of the Innate Immune System

Pattern recognition receptors (PRRs)	<ul style="list-style-type: none"> Toll-like receptors (TLRs), C-type lectin receptors (CLRs), Retinoic acid-inducible gene (RIG)-1-like receptors (RLRs), NOD-like receptors (NLRs)
Antimicrobial peptides	α -Defensins, β -defensins, cathelin, protegrin, granulysin, histatin, secretory leukoprotease inhibitor, and probiotics
Cells	Macrophages, dendritic cells, NK cells, NK-T cells, neutrophils, eosinophils, mast cells, basophils, and epithelial cells
Complement components	Classic and alternative complement pathway
Cytokines	Autocrine, paracrine, endocrine cytokines

Toll-like Receptors (TLRs)

- TLRs are a class of proteins that play a key role in the *innate immune system*. They are single, membrane-spanning, *non-catalytic receptors* usually expressed in sentinel cells such as *macrophages and dendritic cells*, that recognize structurally conserved molecules derived from microbes.
- TLRs are evolutionarily conserved receptors are homologues of the *Drosophila Toll protein*.
- Eleven human** and thirteen murine (mice) TLRs have been characterized.
- In 2011, **Dr. Beutler and Dr. Hoffmann** were awarded the Nobel Prize in Medicine or Physiology for their work on TLR.
- Imiquimod** and its successor **resiquimod**, are ligands for **TLR7 and TLR8**.
- The **lipid A analogon eritoran** acts as a **TLR4 antagonist**. It is being developed as a drug **against severe sepsis**.

Cluster of Differentiation (CD) Marker

- Lymphocytes and other leukocytes have a number of surface antigens or marker
- A marker leucocyte differentiation antigen has been given a CD (cluster of differentiation) number on the bases of reaction with a cluster of monoclonal antibodies.
- These markers reflect the stage of differentiation and functional properties of cell.
- Important cells with their CD markers are:

Primary T-cell associated	CD1, CD3, CD4, CD5, CD8
Primary B-cell associated	CD10, CD19, CD20, CD21, CD23, CD79a
Primary monocyte or macrophage associated	CD11c, CD13, CD14, CD15, CD33, CD64
Primary NK cell associated	CD16, CD56
Primary stem cell and progenitor cell associated	CD34
Activation markers	CD30
Present on all leukocytes	CD45 (PAN leukocytes marker)

Important Facts about CD Markers

- CD3** is *Pan T* cell marker; **CD19** is *Pan B* cell marker (CD Three = Pan T)
- CD1** is required for presentation of *lipid antigens*.
- The most clear cut differentiation between T- and B-cells is by their surface markers. For example, by demonstration of CD3 of T-cells and Ig on B-cells.
- CD-95** is a *death receptor*, member of TNF receptor family. It mediates *apoptosis*.
- CD14 (LPS-receptor)**—receptor for lipopolysaccharide (endotoxin).
- CD45 is called as Leukocyte common antigen (LCA) as it is present in all leukocytes. Important type of CD 45 are:
 - CD45 RA—Medullary T-cells i.e., “naïve” T-cells
 - CD45 RB—All leukocytes
 - CD45 RC—Subset T, medullary thymocytes “naïve”
 - CD 45 RO—Subset T, cortical thymocytes “memory”

Inflammasome

- Large cytoplasmic complexes of intracellular proteins that link the sensing of microbial products and cellular stress to the proteolytic activation of interleukin (IL) 1 β and IL-18 inflammatory cytokines. Activation of molecules in the inflammasome is a key step in the response of the *innate immune system* for intracellular recognition of microbial and other danger signals in both health and pathologic states.
- Diseases a/w **overactive inflammasome** activity:
 - Familial cold autoinflammatory syndrome
 - Familial Mediterranean fever
 - Muckle-Wells syndrome
 - Chronic infantile neurologic cutaneous and articular syndrome (CINCA)

- Pyogenic arthritis, pyoderma gangrenosum, and pseudotumor syndrome (PAPA)
- Vitiligo.

Interferons (IFNs)

These glycoproteins are produced by virus-infected cells.

Properties of Interferon

- α - and β -interferons inhibit viral protein synthesis and viral replication
- γ -interferons promotes MHC1 and 2 expression and antigen presentation in all cells.
- Antitumor activity**
- Activate macrophages and NK cells to *kill virus infected cells*.

Types of Interferons

- α IFN—produced by human *leucocytes*
- β IFN—produced by human *fibroblasts*
- γ IFN—produced by human *T lymphocytes* in reply to antigenic stimulation

Tumor Necrosis Factor (TNF)

- The principal mediator of *host responses to gram-negative bacteria*. May also play a role in the response in other infectious organisms and is a key cytokine in the pathogenesis of multiorgan failure.
- Activates inflammatory leucocytes to kill microbes; stimulates mononuclear phagocytes to produce cytokines, acts as a co stimulator for antibody production and T cell activation by B cells, and exerts an interferon like effect against viruses.
- TRAPS**: Gain-of-function mutations in the TNF- α receptor cause **TNF- α receptor-associated periodic syndrome** (TRAPS), which is characterized by *recurrent fever in the absence of infection*, due to persistent stimulation of the TNF- α receptor.
- TNF- α inhibiting drugs** are: etanercept, infliximab, adalimumab, certolizumab; golinumab.

Important Cytokines

Cytokines	Functions
IL-1	Endogenous pyrogen, causes fever, acute inflammation
IL-6	Endogenous pyrogen
IL-8	Major chemotactic factor for neutrophils

Contd...

Contd...

Cytokines	Functions
IL-12	Induces differentiation of T cells into Th1 cells, activates NK cells, also secreted by B cells
TNF- α	Mediates septic shock, activates endothelium
IL-3	Supports the growth and differentiation of bone marrow stem cells, functions like GM-CSF
IL-2	Stimulates growth of helper and cytotoxic T cells
Interferon- γ	Activates macrophages and Th1 cells, has antiviral and antitumor properties
IL-4	Induces differentiation into Th1 cells. Promotes growth of B cells
IL-5	Promotes differentiation of B cells. Promotes growth of B cells
IL-10	Modulates inflammatory response

Colony Stimulating Factors (CSFs)

- These are involved in directing the division and differentiation of bone marrow stem cells, and the precursors of blood leucocytes.

Complement Pathways

- Ehrlich** coined the term **complement**.
- Classical** complement pathway initiated by **Ag-Ab complexes** (IgM and IgG)
- Alternate** pathway initiated by **endotoxin**: Bacterial cell wall (IgA complexes)
- The **central process** in the complement pathway is the **conversion of C3 to C3b**.
- Opsonins: C3b and IgG are the two primary opsonins in bacterial defense; C3b also helps clear immune complexes.

Deficiency of	Disorder
C1 esterase inhibitor	Hereditary angioedema (due to uncontrolled complement activation); ACE inhibitors are contraindicated
C1, C2, C4	Immune complex disease (e.g. SLE, HSP)
C3 and C3b inactivator	Recurrent pyogenic bacterial infections , \uparrow susceptibility to type III hypersensitivity reactions

Contd...

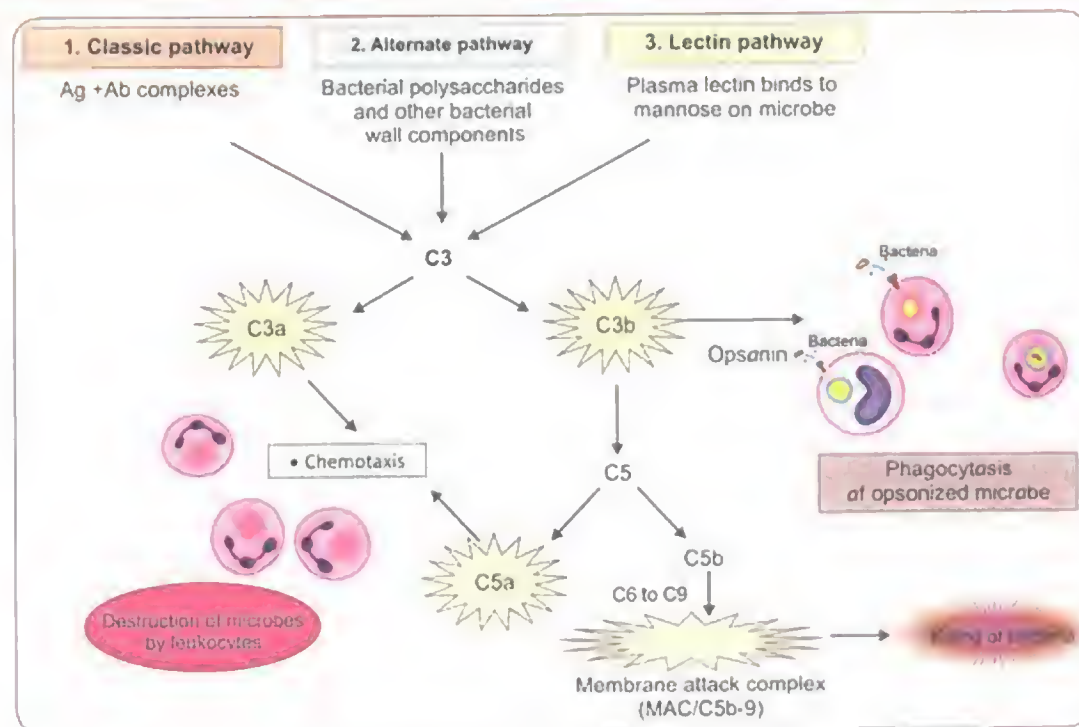


Fig. 8.1: Different pathways of activation and functions of the complement system

Contd ...

Deficiency of	Disorder
C5b-C9 (membrane attack complex)	<i>Neisserial</i> infection, toxoplasmosis
Decay accelerating factor (DAF, GPI anchored enzyme)	Complement mediated lysis of RBCs and <i>paroxysmal nocturnal hemoglobinuria</i>

EXTRA EDGE

- Icatibant* is a **bradykinin B2 receptor antagonist** approved for treating acute attacks of hereditary angioedema.

Immunoglobulin/Antibody Structure and Function

- Fab:** antigen binding fragment
- Fc:** Constant, Carboxy terminal, Complement binding (IgG and IgM only), Carbohydrate side chains.
- Variable part of L and H chains recognizes antigens. Heavy chain contributes to Fc and Fab fragments. Light chain contributes only to Fab fragment

- Papain digestion** yields two univalent Fab fragments and one Fc fragment.
- Pepsin digestion** yields a bivalent Fab fragment.

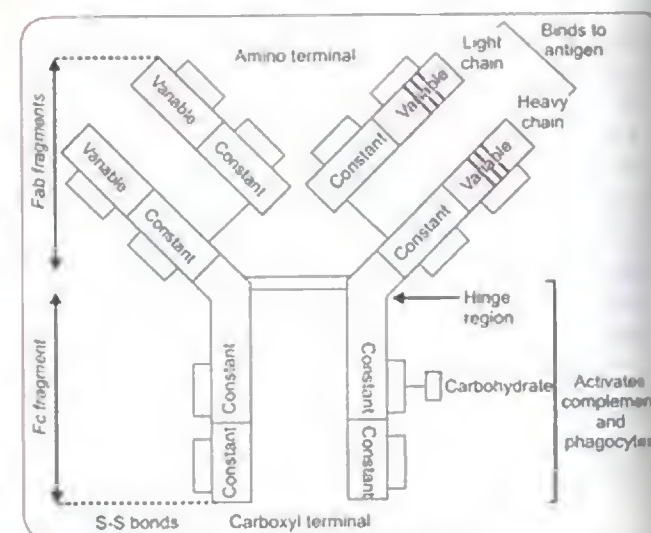


Fig. 8.2: Schematic representation of an IgG molecule, indicating the location of the constant and the variable regions on the light and heavy chains

Immunoglobulin (Ig) Isotypes

- IgG:**
 - Most abundant** Ig (80%), distributed in blood and interstitial fluids
 - Main Ig in **secondary immune response**
 - ONLY** Ig that **crosses placenta**, so the **major protective Ig in neonate**
 - Opsonises bacteria**, neutralizes bacterial toxins and viruses, coats cells prior to killing by killer cells
 - Activates complement** via **classical** pathway
- IgA:**
 - Principal Ig in **secretions** of respiratory and GI tract and in sweat, saliva, tears and colostrums
 - Key **defense for mucosal surfaces** – prevents attachment of bacteria and viruses to mucosa
 - J (joining) chain is seen in dimeric forms of IgA, it is synthesized by plasma cells
 - IgA activates complement** via **Alternate** pathway
- IgM:**
 - Macroglobulin** made up of 5 monomeric Ig subunits linked by a J chain – **Massive**, **Max.** mol. weight
 - Mainly **intravascular**
 - Major Ig of **primary** immune response (**primary = IgM**)
 - Does not cross placenta, fetal production of high levels of IgM may be of diagnostic significance (e.g. rubella)
 - Activates complement** via **classical** pathway
 - Blood group** antibodies are IgM
- IgD:**
 - Unclear function
 - Found on **surface of many B cells** and in serum
- IgE:**
 - Produced in linings of intestine and respiratory tract; mostly distributed extravascularly
 - Cannot cross placental barrier; **cannot** fix complement
 - ONLY** heat labile immunoglobulin

Hypersensitivity Reactions (Coombs and Gel Classification)

Type	Name	Examples
Type 1	Anaphylactic reaction. Mediated by IgE	<ul style="list-style-type: none"> Anaphylaxis Atopic asthma Angioedema Allergic rhinitis, Urticaria, hay fever
Type 2	Cytotoxic Cytolytic reaction. Antibody mediated. Mediated by IgG and IgM "Cytotoxic"	<ul style="list-style-type: none"> Transfusion reaction Hemolytic anemia (quinine, penicillin) Erythroblastosis fetalis Certain drug reactions Goodpasture syndrome Myasthenia gravis ITP Rheumatic fever
Type 3	Immune complex reaction. Antigen antibody complex activates complement	<ul style="list-style-type: none"> Acute serum sickness (large amounts of foreign serum) Chronic serum sickness—SLE Arthus reaction Certain forms of acute glomerulonephritis Hypersensitivity pneumonitis Type 2 Leprosy reaction (ENL)
Type 4	Delayed hypersensitivity. Cell mediated reaction. T cell mediated (initiated by CD4+ T-cells)	<ul style="list-style-type: none"> Mantoux test Tuberculoid-leprosy. Contact dermatitis Transplant rejection (graft versus host disease) Multiple sclerosis, Guillain-Barre syndrome, Hashimoto's thyroiditis

Mnemonic: "ACID" = Types 1, 2, 3, 4 Hypersensitivity reactions.

Types of Grafts

- **Heterotopic:** Graft placed in a *different type of tissue* e.g.: thyroid tissue in subcutaneous pocket
- **Isotopic:** Graft placed in the *same anatomical location* of tissue from which the graft came
- **Orthotopic:** Graft placed in same type of tissue as graft origin, but a *different anatomical position* e.g.: skin grafted from thigh to arm.

Classification of Transplant Rejection

Type	Time	Pathological findings	Mechanism	Treatment
Hyperacute rejection	Minutes to hours	Thrombosis, necrosis	Preformed antibody and complement activation (type II hypersensitivity)	None—Rapid and irreversible graft loss
Acute vascular rejection	5–30 days	Vasculitis	Antibody and complement activation	Increase immunosuppression
Acute cellular rejection	5–30 days	Cellular infiltration	CD4+ and CD8+ T cells (type IV hypersensitivity)	Increase immunosuppression
Chronic allograft failure	> 30 days	Fibrosis, scarring	Immune and non-immune mechanisms	Minimize drug toxicity, control high BP and hyperlipidemia

Domino Transplantation

- This occurs when an organ is removed from a transplant recipient, which is *suitable for use as a graft in another patient*.
- **Classic example:** in *cystic fibrosis*, when the traditional operation was a heart/double lung en-bloc operation; the recipient's heart was removed when in fact it worked pretty well and so could be used to transplant another heart only patient.

Major Histocompatibility Complex (MHC)

- MHC encoded by Human Leucocyte Antigens (HLA) genes located on **short arm of Chromosome 6 (6p)**.
- MHC Proteins *present peptide antigens on cell surfaces for recognition by T-Cell receptors*.

MHC 1	MHC 2
<ul style="list-style-type: none"> • MHC 1 (Class 1) = HLA-A, HLA-B, and HLA-C. • MHC 1 antigens are expressed on <i>all nucleated cells and platelets except mature RBCs</i> • Antigen is loaded in RER of mostly intracellular peptides • Mediates viral immunity • Pairs with β2-microglobulin • Responding T-cells are predominantly of the CD8 class 	<ul style="list-style-type: none"> • MHC 2 (Class 2) = HLA-DP, HLA-DQ, HLA-DR. • MHC 2 antigens expressed only on 'antigen presenting cells' (APCs), including dendritic cells, macrophages, B cells and activated T-cells. • Antigen is loaded in an acidified endosome. • Responding T-cells are predominantly CD4.

Autograft	From <i>self</i>
Syngenic graft/ Isograft	From <i>identical twin</i> or clone (i.e., genetically identical with recipient)
Allograft/homograft	From non-identical member of <i>same species</i>
Xenograft	From <i>different species</i>

EXTRA EDGE

- **"Rule of 8":** "CD8 = 8X1 (class 1) = 8"; "CD4 = 4X2 (class 2) = 8"

HLA Subtypes and Associated Diseases

HLA	Associated Diseases
B27	Psoriatic arthritis, Ankylosing spondylitis, Reiter's syndrome, Reactive arthritis (<i>Yersinia</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Cholera</i>), Acute anterior uveitis
B8	Myasthenia Gravis
B47	Congenital adrenal hyperplasia
B51, B5	Behcet's disease
B57	Abacavir hypersensitivity
B8, DR3	Graves' disease
DR2	Multiple sclerosis, Goodpasture syndrome, Narcolepsy
DR3	Sjogren's syndrome, Adrenal insufficiency, Dermatitis herpetiformis, Chronic active hepatitis, SLE
DQ8, DR4	Type 1 diabetes mellitus (IDDM)
DR4, DQ1	Pemphigus vulgaris

Contd

(cont)

HLA	Associated Diseases
DR4	Rheumatoid Arthritis
DR5	Pernicious anemia, Hashimoto's thyroiditis, Scleroderma
DR7	Steroid responsive nephrotic syndrome
DQ2	Gluten sensitive enteropathy (celiac sprue)

Antigen-Presenting Cells (APC)

Professional APCs	Non - professional (amateur) APCs
They express MHC class II molecules on the cell surface	They do NOT express MHC class II molecules; they are stimulated by IFN- γ
<ul style="list-style-type: none"> • Dendritic Cells <ul style="list-style-type: none"> • Follicular Dendritic cells • Interdigitating dendritic cells • Langerhans cells • Macrophages • Monocytes • B cells 	<ul style="list-style-type: none"> • Fibroblasts • Keratinocytes • Thymic epithelial cells • Thyroid epithelial cells • Glial cells (brain) • Pancreatic beta cells • Endothelial cells • M cells (microfold cells) in GIT mucosa

EXTRA EDGE

- Mature dendritic cells are the **most potent** antigen presenting cells.
- Immature dendritic cells are called "**veiled cells**" since they have cytoplasmic veils instead of dendrites.

PRIMARY IMMUNODEFICIENCY DISEASES

B-Cell Disorders

- Pathogens are **pyogenic bacteria** (e.g. staphylococci, streptococci, H. influenzae and pneumococci), yeasts, giardia and campylobacter.
- Viruses a/w B-cell disorders are: **Enterovirus** (ECHO, Coxsackie viruses) and **Rotavirus**.
- Treated with IV gammaglobulin.

Bruton's X-linked agammaglobulinemia

- Presents in **Boys** only at about 6 months with recurrent pyogenic and gastrointestinal infections, autoimmune disorders and lymphoreticular malignancies.
- NO circulating **B** cells: $\downarrow\downarrow$ IgG; absent IgM, IgA, IgD, IgE
- **Normal T-cell function**, i.e. normal delayed hypersensitivity

Common variable immunodeficiency

- Also known as **late onset** hypogammaglobulinemia because it manifests *only by 15 - 35 years* of age
- Recurrent pulmonary infections and chronic diarrhea (malabsorption and giardiasis); \uparrow of autoimmune disorders
- \downarrow serum Ig levels: cell mediated immunity normal in 60%.

Dysgammaglobulinemia (selective Ig deficiencies)

- **Selective IgA deficiency** is the **MC** condition in this group
- Selective IgM deficiency is associated with septicemia.
- Deficiency of IgG2 has been observed in *chronic progressive bronchiectasis*

Acquired hypogammaglobulinemia

- Presents in infancy/childhood
- Associated conditions include autoimmune disorders, hemolytic anemia and thymoma. IgG <250 mg/dl; IgM may be spared. Often normal B cell count. Variable abnormalities in cell mediated immunity

Transient hypogammaglobulinemia of infancy

- Usually presents between 3 and 6 months of age
- Occurs when the onset of Ig synthesis (especially IgG) is delayed beyond the normal time

T-Cell Disorders

- Opportunistic infections (e.g. pneumocystis carinii, fungi) severe viral and chronic bacterial infections, e.g. TB
- Treatment by: thymus grafts; bone marrow transplantation.

Congenital thymic aplasia (Di George syndrome)

- Developmental defect involving the **3rd and 4th pharyngeal pouches** causing **absence of thymus**.
- A.k.a **22q11.2 deletion** syndrome; **velo-cordio-facial** syndrome; **Cotch 22** syndrome.
- Presents in infancy/adulthood with cardiovascular defects (**Fallot's tetralogy**), **hypoparathyroidism** (neonatal tetany), **convulsions** and opportunistic infections. **Characteristic asymmetric "crying facies"** is present. Variable reduction in T-cell number and function. B-cell function, i.e. antibody levels are normal.

Chronic mucocutaneous candidiasis

- Some cases are familial
- Severe Candida infection of the skin, mucus membranes and nails with associated endocrine abnormalities, e.g. **hypoparathyroidism**
- Negative skin testing for Candida.

Combined B- and T-Cell Disorders

- Pathogens are pyogenic bacteria, fungi, and TB, and Pneumocystis carinii.
- Treatment by bone marrow transplantation.

Severe Combined Immuno-Deficiency

- Mostly AR inheritance: 50% are deficient in enzyme **adenosine deaminase (ADA)** "**SCID affects KIDS**"!
 - Presents in **first few months of life** with failure to thrive, recurrent pneumonia, chronic diarrhea and widespread candidiasis.
 - Complete absence of B- and T-cell immunity.
- Note:** Unconnected to this topic, but also know that, **adenosine deaminase** is elevated in **TB pleuritis and peritonitis**.

Ataxia telangiectasia

- AR, presents in infancy with **cerebellar ataxia, oculocutaneous telangiectasia** and recurrent **sinopulmonary infections**.
- Higher incidence of malignancy, especially **lymphomas**.
- Low IgA and IgE levels. T-cell deficiency is variable.

Wiskott-Aldrich syndrome

- **XLR** disease characterized by **severe eczema, thrombocytopenia** and **recurrent pyogenic infections**, e.g. *Str. pneumoniae*, *H. influenzae*, *N. meningitidis*.
- Increased incidence of lymphoreticular malignancies
- IgM level is low, but IgG and IgA levels are normal or elevated.

Neutrophil/Phagocytic Disorders

- Pathogens are gram -ve (e.g. *E. coli* and *Klebsiella*) and gram +ve (e.g. *Staph. aureus*) bacteria, some viruses and fungi (*Aspergillus*).
- Treatment is with antibiotics.

Chronic granulomatous disease

- X-linked defect in the **NADPH oxidase** system (occasionally AR).

Contd..

Contd...

- Presents in first 2 years of life with recurrent bacterial infections, lymphadenopathy, hepatomegaly, pneumonia, osteomyelitis and abscesses. Highly susceptible to *Aspergillus* infections.
- **Impaired opsonization** and bactericidal activity; ↓ hydrogen peroxide production appears to be the major reason for the bactericidal defect (**nitroblue tetrazolium test** - screening method).
- Humoral and cellular immune responses are normal.
- May respond to **IFN-γ treatment**.

Chediak-Higashi syndrome

- AR, very rare **deficiency of NADH or NADPH oxidase** in the polymorphonuclear cells.
- Presents with **oculocutaneous albinism, thrombocytopenia** and bacterial infections (*Neisseria*). There are giant **peroxidase positive inclusions** in the cytoplasm of leucocytes.
- **Reduced chemotaxis** and **phagolysosome fusion**

Leukocyte adhesion deficiency

- AR; **defect in LFA-1 integrin** proteins on phagocytes.
- **Failure of neutrophils to migrate** to the site of infection.
- Presents early with recurrent bacterial infections, absent pus formation and delayed separation of umbilicus

Hyper IgE-Recurrent Infection Syndrome, (Job's Syndrome)

- AD; Reduced chemotaxis, reduced suppressor T cell activity
- Eczematoid or pruritic dermatitis, "cold" skin abscesses, recurrent pneumonias with *S. aureus* with bronchopleural fistulae and cyst formation, mild eosinophilia, mucocutaneous candidiasis, characteristic facies, restrictive lung disease, scoliosis, delayed primary dental decudation

RECOMBINANT CYTOKINES AND CLINICAL USES

Agents	Clinical uses
Aldesleukin (IL-2)	Renal cell ca, metastatic melanoma
Erythropoetin (epoetin)	Anemias, esp. in renal failure
Filgrastim (granulocyte-colony stimulating factor)	Recovery of bone marrow
Sargramostim (granulocyte macrophage-CSF)	Recovery of bone marrow
Alpha interferon	Hepatitis B and C, Kaposi's sarcoma, leukemia's, malignant melanoma
Beta Interferon	Multiple sclerosis
Gamma Interferon	Chronic granulomatous disease
Oprelvekin (IL-11)	Thrombocytopenia
Thrombopoietin	Thrombocytopenia

THERAPEUTIC ANTIBODIES

Drugs	Target	Clinical uses
(suffix—"zumab")		
Daclizumab	IL-2 receptor	Prevent acute rejection of renal transplant
Omalizumab	IgE	Additional line of treatment for severe asthma
Pavilizumab	RSV F protein	Respiratory syncytial virus
Ecilizumab	C5	Paroxysmal nocturnal hemoglobinuria
Trastuzumab (Herceptin)	erb-B2	HER-2-overexpressing breast cancer
Certolizumab	TNF-α signaling	Crohn's disease
Bevacizumab	VEGF	Colorectal cancer; Age related macular degeneration
Ranibizumab	VEGF-A	Age related macular degeneration
Gemtuzumab	CD33	AML
Natalizumab	Alpha 4 integrin	Multiple sclerosis and Crohn's disease
Alemtuzumab	CD52	CLL
Pembrolizumab	PD-1	Melanoma
Teclistumab	IL-17	Psoriasis
(suffix—"mumab")		
Adalimumab	TNF-α	Crohn's disease, rheumatoid arthritis, psoriatic arthritis
Panitumumab	EGFR	Colon cancer
Ipilimumab	CTLA-4	Melanoma
Denosumab	RANK ligand	Breast, prostate cancer
Oritumumab	CD 20	CLL
Ustekinumab	IL-12 and IL-23	Psoriatic arthritis
Secukinumab, Brodalumab	IL-17	Psoriatic arthritis
(suffix—"ximab")		
Aliciximab	Glycoprotein IIb/IIIa	Prevent cardiac ischemia in unstable angina and in patients treated with percutaneous coronary intervention
Rituximab	CD20	B-cell non-Hodgkin's lymphoma; rheumatoid arthritis
Infliximab	TNF-α	Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Cetuximab	EGF receptor	Colorectal cancer; head and neck cancer
Beasiximab	CD25 (IL-2R)	Transplant rejection
Digoxin immune Fab	Digoxin	Antidote for digoxin overdose
Rituximab vedotin	CD 30	Hodgkin's disease, anaplastic lymphoma
(suffix - "omab")		
Tositumomab, Ibritumomab	CD20	Non-Hodgkin's lymphoma

Note

Various drugs including rituximab, bevacizumab, pavilizumab etc... have been asked in various recent exams like AIIMS, PGI, JIPMER and NEET - please be sure to read this table.

IMMUNOSUPPRESSIVE DRUGS

Drug	Mechanism	Indication	Adverse effects
Cyclosporine	Binds to cyclophilins. Complex blocks the differentiation and activation of T-cells by inhibiting calcineurin, thus preventing the production of IL-2 and its receptor. (Helper T-cell inhibition)	Rejection prevention after transplantation; selected autoimmune disorders	Nephrotoxicity (preventable with mannitol diuresis), tremor, hirsutism, HTN, hypomagnesemia, gum hyperplasia, predisposes patient to viral infections and lymphoma; NOT myelosuppressive
Sirolimus (Rapamycin)	Binds to mTOR; inhibits T-cell proliferation in response to IL-2	Rejection prevention	Thrombocytopenia, hyperlipidemia
Azathioprine	Antimetabolite precursor of 6-MP that interferes with the metabolism and synthesis of nucleic acids; toxic to proliferating lymphocytes	Autoimmune disorders (including glomerulonephritis and hemolytic anemia), rejection prevention after kidney transplantation	Leukopenia
Mycophenolic acid	Inhibits de novo guanine synthesis and blocks lymphocyte production	Rejection prevention after transplantation	Leukopenia, GI toxicity
Tacrolimus (FK-506)	Similar to cyclosporine; binds to FK-binding protein inhibiting secretion of IL-2 and other cytokines	Rejection prevention after transplantation and reversal of rejection	Nephrotoxicity, peripheral neuropathy, HTN, pleural effusion, hyperglycemia
Thalidomide	Inhibits T-cell function and migration	Chronic graft versus host disease (GVHD)	Sedation (was historically used as a sedative), constipation, teratogenic (seal limbs-phocomelia); peripheral neuropathy
Muromonab-CD3 (OKT3)	Monoclonal antibody that binds to CD3 (epsilon chain) on the surface of T-cells; blocks cellular interaction with CD3 protein responsible for T-cell signal transduction	Rejection reversal and early rejection maintenance	Induces one-time cytokine release syndrome (fever, bronchospasm, leukopenia); limited to short-term therapy
Antithymocyte globulin (thymoglobulin)	Polyclonal antibody that depletes T-cell population	Rejection reversal and early rejection maintenance	Limited to short-term therapy , serum sickness
Hydroxy-chloroquine	Inhibits antigen processing	Chronic GVHD	Visual disturbances, bulls eye retinopathy

(AVN: avascular necrosis; HTN: hypertension)

CHAPTER
9

Pharmacology

BASICS OF PHARMACOLOGY

Routes of Drug Administration

- **Oral** (most drugs)
- **Sublingual** or **buccal** (glyceryl trinitrate/nitroglycerin, buprenorphine, desamino oxytocin, nifedipine in emergencies)—**non-ionic highly lipid soluble** drugs
- **Rectal** (paracetamol; diazepam, indomethacin, ergotamine)
- **Cutaneous patches** (transdermal—fentanyl, GTN, nicotine, estradiol, clonidine)
- **Inhalation** (anesthetics)
- **Nasal** (GnRH agonist, desmopressin)
- **Pareuteral** (SC, IM, IV, Intradermal)

Therapeutic Window Phenomenon

- Best possible therapeutic effect is exerted only in a narrow range of drug concentrations or drug doses. Both above and below this range, beneficial effects are suboptimal i.e. the effect declines if the doses are increased beyond a certain level. Examples:
 - **Tricyclics** (Imipramine etc.) = 50–150 ng/ml
 - **Clonidine** = 0.2–2 ng/ml
 - **Glipizide** = <25 mg/day.

Adverse Drug Reactions (ADRs)

Type A (Augmented) Reactions	Type B (Bizarre) Reactions
<ul style="list-style-type: none"> • Due to exaggeration of an intended pharmacologic action of the drug, predictable • Ex: increased bleeding with anticoagulants or bone marrow suppression with anti-neoplastics. • These are more common, often dose-dependent and mostly preventable and reversible. 	<ul style="list-style-type: none"> • Are often more severe adverse effects unrelated to the known pharmacologic action of the drug, Unpredictable • Ex: most immunologic reactions, allergy and idiosyncrasy (anaphylactic reaction to penicillin.) • These are less common, not dose related, may require withdrawal of the drug.

First Order (Exponential) Kinetics

- The rate of elimination is directly proportional to the drug concentration
- **Clearance** remains constant
- A constant fraction of the drug present in the body is **eliminated in unit time**.

Zero-order (linear) kinetics

- The **rate of elimination remains constant irrespective of drug concentration**
- **Clearance decreases** with increase in concentration
- A constant amount of the drug is eliminated in unit time. Examples:
 - Phenytoin
 - Aspirin (salicylates)
 - Ethyl alcohol
 - Warfarin
 - Tobutamide
 - Theophylline
 - Propafenone

Synergism

When the action of one drug is facilitated by another, they are said to be synergistic. Synergism can be:

1. **Additive:** The effect of two drugs is in the same direction and simply adds up, i.e.
Effect of drugs A + B = Effect of drug A + effect of drug B

Additive drug combinations

Aspirin + Paracetamol (as analgesic/antipyretic)
Nitrous oxide + halothane (as general anesthetic)
Amlodipine + atenolol (as antihypertensive)
Glibenclamide + metformin (as hypoglycemic)
Ephedrine + theophylline (as bronchodilator)

- Side effects of the components of an additive pair may be different - do not add up. Thus, the combination is better tolerated than the higher dose of one component.
- 2. **Supra-additive (potentiation):** The effect of combination is greater than the individual effects of the components.

Effect of drugs A + B > effect of drug A + effect of drug B
This is always the case when one component is inactive as such.

Supra additive drug combinations

Drug pair	Basis of potentiation
Actylcholine + physostigmine	Inhibition of breakdown
Levodopa + carbidopa/benserazide	Inhibition of peripheral metabolism
Adrenaline + cocaine/desipramine	Inhibition of neuronal uptake
Sulfamethoxazole + trimethoprim	Sequential blockade
Antihypertensives (enalapril + hydrochlorothiazide)	Tackling two contributory factors
Tyramine + MAO inhibitors	Increasing releasable CA store

EXTRA EDGE

- Two **bactericidal drugs** are frequently **additive and sometimes synergistic** if the organism is sensitive to both, e.g.:
 - Penicillin/**ampicillin** + streptomycin/**gentamicin** for enterococcal SABE.
 - Penicillins by acting on the cell wall may **enhance the penetration of the aminoglycoside** into the bacterium.

Hepatic Microsomal Enzyme Inducers

- Alcohol (chronic use)
- Barbiturates: phenobarbitone, pentobarbitone, secobarbitone
- Carbamazepine
- Glutethimide
- Griseofulvin
- Marijuana smoke
- Meprobamate
- Phenytoin
- Primidone
- Rifampin**
- Sulfinpyrazone
- Tobacco smoke.

EXTRA EDGE

- CYP3A4** is the **most abundant** isoform of cytochrome P450 (CYP) in adult human liver.

Intravenous Infusion Solutions to Avoid

- Dextrose:** Avoid furosemide, ampicillin, hydralazine, insulin, melphalan, quinine.
- 0.9% saline:** Avoid amphotericin, lignocaine, nitroprusside.

Drugs Undergoing Enterohepatic Circulation

- Erythromycin
- Ampicillin
- Rifampicin
- Tetracycline
- OCP's
- Phenolphthalein (EARTOP)

Hit and Run Drugs

- Drugs whose effects last much longer than the drug itself:
 - Reserpine
 - Guanethidine
 - MAO inhibitors
 - Omeprazole.

Schedules of Drugs

- As per **Drugs and Cosmetics Act (1945, amended in 2001)**, there are schedules from A to Y, which govern the drugs. Some important schedules in common usage are given below
- Schedule H:** Drugs which must be sold only with prescription of a registered medical practitioner.
- Schedule M:** Deals with GMP (Good Manufacturing Practices) and requirements of premises, plant/factory and equipment.
- Schedule P:** deals with 'expiry period' of medicines.
- Schedule W:** drugs shall be marketed under generic names only.
- Schedule X:** Psychotropic drugs requiring special licenses for manufacture and sale.
- Schedule Y:** specifies requirements and guidelines on clinical trials, import and manufacture of new drugs.

BASICS OF CLINICAL RESEARCH

Stages of Evidence in Trials/Research

Grade	Evidence	Reliability
Grade I	Systematic review or metaanalysis of all relevant randomized controlled trials (RCTs)	Most reliable, may form the basis of clinical decisions
Grade II	Well powered randomized controlled trial/more than one	Reliable, but maybe supported or refuted by other studies
Grade III	Open label trials/pilot studies/observational (cohort and case control) studies (prospective or retrospective)	Less reliable, need more rigorous testing, may indicate further investigation
Grade IV	Case reports/anecdotal reports/clinical experience	Least reliable, may serve as pointers to initiate formal studies

EXTRA EDGE

- Declaration of Helsinki:** The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of **ethical principles for medical research involving human subjects**, including research on identifiable human material and data (1964).

Stages of Clinical Trials

Phase	Description	Subjects
II	<ul style="list-style-type: none"> Micro-dosing study (exploratory Investigational New Drug study). Sub-therapeutic doses of the drug are given to establish whether the new agent will work similarly in humans as it has worked in previously conducted in-vivo safety, pharmacology and toxicology preclinical trials. It reduces the cost and time of drug development process. 	< 20 subjects over usually 7 days (<i>healthy volunteers</i>)
I	<ul style="list-style-type: none"> Human pharmacology (tolerability, pharmacodynamics, pharmacokinetics) and safety assessment 	< 100 subjects (<i>healthy volunteers</i>)
I	<ul style="list-style-type: none"> Therapeutic exploration and dose ranging <ul style="list-style-type: none"> 2A: to establish dosing 2B: to establish efficacy 	< 300 patients with disease
I	<ul style="list-style-type: none"> Therapeutic confirmation/comparison. To determine effectiveness Vs current gold standard. Usually randomised clinical trials (RCT). Once Phase 3 trials are completed, the company can file a "New drug application" for approval by regulatory authorities (ex: Drug Controller General of India, DCGI). 	1000–300 patients with disease (<i>large numbers</i> required for RCT)
4	<ul style="list-style-type: none"> Post-marketing surveillance to detect side effects and further studies continue to assess effectiveness (ex: in different populations) 	1000s of patients already using the drug

EXTRA EDGE

- Phase 0 and Phase 4 may **not always** be performed.

Orphan Drugs

- Sometimes, the drug is not developed into a usable medicine, because the costs incurred will not be recovered by the developer. As a result the market economy is liable to leave some **rare diseases** untreated (for some uncommon diseases). Such a disease is called an **orphan disease** and the drug - an **orphan drug** and the sufferer is an **orphan patient**.
- For such drugs, development still occurs due to government offered incentives and tax reliefs to the pharma company.
- Examples** of orphan drugs: Acetyl cysteine (for paracetamol poisoning); Anagrelide (for polycythemia vera) etc.

Pharmacovigilance

- Pharmacovigilance** means to remain vigilant and observe the adverse effects of drugs by continuously monitoring for unwanted effects and other safety related aspects of marketed drugs. **PMS** (Post Marketing Surveillance) or **PASS** (Post Approval Surveillance Studies) contribute to pharmacovigilance.
- PSUR:** Periodic Safety Update Reports - After release of the drug, for the first 2 years, every 6 months and for the next 2 years, annually, (i.e. totally 4 years) the manufacturer has to submit the PSUR to the authorities

EXTRA EDGE

- Efflux transporters such as P-glycoprotein play an important role in drug transport in many organs. In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption.
- INHIBITORS of p-glycoprotein** are: ketoconazole, amiodarone, verapamil, ticagrelor, erythromycin, clarithromycin, ritonavir, quinidine, probenecid, cimetidine.

AUTONOMIC NERVOUS SYSTEM (ANS)

Neurotransmitters of ANS

	Sympathetic	Para-sympathetic
Preganglionic	ACh	ACh
Postganglionic	NA	ACh

CHOLINERGIC SYSTEM

Drug	Clinical Applications	Action
Direct agonists		
Bethanechol	Postop and neurogenic ileus and urinary retention	Activates Bowel and Bladder smooth muscle; resistant to BOTH true and pseudo AChE.
Carbachol	Glaucoma (not routinely used), pupillary constriction and ↓ of IOP	
Pilocarpine	Potent stimulator of tears, saliva, ↓ IOP	Glaucoma
Methacholine	Challenge test for diagnosis of asthma	Stimulates muscarinic receptors in airway when inhaled
Anticholinesterases (reversible)		
Neostigmine	Postop and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postop); has quaternary amine N ⁺ and is lipid insoluble → DOES NOT penetrate CNS	↑ endogenous ACh; NO CNS penetration.
Pyridostigmine	Myasthenia gravis (long acting); DOES NOT penetrate CNS	↑ endogenous ACh, ↓ strength
Edrophonium	Diagnosis of myasthenia gravis (extremely short acting) – Tensilon test	↑ endogenous ACh
Physostigmine	Glaucoma (not routinely used); has tertiary amine N⁺ and is lipid soluble → CROSSES blood brain barrier, antidote for atropine/belladonna toxicity	↑ endogenous ACh
Echthiophate	Glaucoma (not routinely used)	
Rivastigmine, donepezil, galantamine	have been found to improve cognitive defects in Alzheimer's disease ; (<i>Tacrine</i> - liver damage - no longer used).	Reversible anticholinesterases that cross the blood brain barrier. By increasing brain acetylcholine levels , improve symptoms of Alzheimer's

- Therapeutic use of Acetyl choline is NOT possible because it is rapidly degraded.
 - **Hemicholinium** blocks choline uptake (**rate limiting step** in acetylcholine synthesis).
 - Transport of ACh into synaptic vesicles is blocked by **vesamicol**.
 - **Botulinum toxin** inhibits ACh release, while **black widow spider toxin** induces massive release and depletion.
 - **True** acetylcholinesterase is present in all cholinergic sites, RBC, gray matter.
- **Pseudo (Butyryl) cholinesterase** is present in plasma, liver, intestine and white matter.
 - Acetylcholine injected IV **does not** penetrate the blood brain barrier.
 - **Methacholine** has a selective action on CVS, was occasionally used to terminate PSVT.
 - In **Mushroom Poisoning**: Phalloidin type (Late mushroom poisoning) **thioctic acid** may have some antidotal effect.

- Of the three types of **muscarinic** receptors; M1 predominates in CNS; M2 in heart; M3 in smooth muscle and glands.
- M1 agonist = **oxotremorine**; M2 agonist = **Methacholine**; M3 agonist = **Bethanechol**

ANTI-CHOLINESTERASE POISONING

Reversible

- **Carbamates**—Physostigmine, neostigmine, pyridostigmine, ambenonium, edrophonium, demecarium

Irreversible

- **Organophosphates**: Dyflos (DFP), echothiophate; parathion, malathion, diazinon (all insecticides); **tabun, sarin, cyclosarin, soman** (nerve gases for **chemical warfare**).
- **Carbamates**: carbaryl, propoxur (both are insecticides).

Symptoms

- ↑ **Secretions** (Diarrhea, Urination, Lacrimation, Sweating, Salivation); Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscle and CNS.

Treatment

- **Atropine IV (muscarinic antagonist)** and Cholinesterase reactivators (**Pralidoxime**, 2-PAM) is a **specific antidote** that reverses **organophosphate** binding to the cholinesterase enzyme (**not useful for carbamate poisons**).

Anticholinergic Drugs (Parasympatholytic, Muscarinic Antagonists)

Drug	Organ system	Use
Atropine and homatropine (long acting),	Eye	Produces mydriasis, cycloplegia; used for refraction in children , in uveitis , corneal ulcers
Tropicamide (shortest acting)	Eye	Tropicamide unreliable cycloplegic; used for fundus examination , pupil dilation preoperatively
Benztropine	CNS	Parkinson's disease
Scopolamine (hyoscine)	CNS	Motion sickness
Ipratropium	Respiratory	Inhalational agent for bronchial asthma , COPD (more effective)

Drug	Organ system	Use
Glycopyrrrolate	GIT	Peanesthetic medication
Oxybutynin	Genito-urinary	↓ urgency in mild cystitis and reduce bladder spasms
Pirenzepine, Prapanteline	GIT	Peptic ulcer , selectively blocks M1 muscarinic receptors and inhibits gastric secretion
Oxybutnin, tolterodine, flavoxate (vesica-selective)	Bladder	Urinary bladder symptoms (relaxes vesical smooth muscles)

Atropine

- Eye: ↑ pupil dilation (**mydriasis**), **cycloplegia**
- Respiratory: ↓ secretions
- Stomach: ↓ acid secretions
- Gut: ↓ motility
- Bladder: ↓ urgency in cystitis

Toxicity

- It **decreases glandular secretions** (sweat, saliva, tracheobronchial, lacrimal secretion—M3 blockade; acid secretion in stomach—M1 blockade), but intestinal and pancreatic secretions, bile and milk secretion are **not** affected.
- Body temperature, tachycardia pulse, dry mouth, dry flushed skin, cycloplegia, constipation, disorientation.
- Can cause **acute angle closure glaucoma** in eyes with narrow angles, **urinary retention** in elderly men with BPH, **hyperthermia** in infants.
- **"Hot as a Hare (hyperthermia); Red as a Beet (flushed skin); Dry as a Bone (↓ secretions); Blind as a Bat (cycloplegia); Mad as a Hatter (disorientation)"**.

ADRENERGIC SYSTEM

Endogenous Catecholamines (CAs)

1. **Noradrenaline (NA)** (Norepinephrine) is the neurotransmitter of the postganglionic sympathetic neurons.
2. **Adrenaline (Adr)** (Epinephrine) is secreted by the adrenal medulla and may have a transmitter role in the brain.
3. **Dopamine (DA)** is a major transmitter in the basal ganglia, limbic system, CTZ, anterior pituitary etc.

Synthesis of CAs

- CAs are synthesised from the amino acid *phenylalanine*.
 - Phenylalanine → Tyrosine → DOPA
 - Dopamine → Noradrenaline → Adrenaline.
- *Tyrosine hydroxylase* is the **rate-limiting enzyme**.
- *Synthesis of adrenaline* occurs **ONLY IN the adrenal medullary cells** and requires high concentration of glucocorticoids through intra-adrenal portal circulation for induction of the **methylating enzyme** (PNMT—phenylethanolamine-N-methyltransferase)

Uptake of CAs

- **Axonal uptake** is important mechanism for terminating the post junctional action of NA and is **inhibited by cocaine, desipramine and its congeners, ephedrine, guanethidine and many H1 antihistaminics**.
- **Granular uptake** is inhibited by reserpine.

Endproducts of Metabolism

- The metanephrines and 4-hydroxy-3-methoxymandelic acid (**VMA**-vanillylmandelic acid) are the major endproducts of **NA and Adr metabolism**.
- **Homovanillic acid (HVA)** is the endproduct of dopamine metabolism.

Types of β Receptors

	β1	β2
Location	Heart, JG cells in kidney	Bronchi, blood vessels, uterus, GIT, urinary tract, eye
Selective agonist	Dobutamine	Salbutamol, terbutaline
Selective antagonist	Metoprolol, atenolol	α-methyl propranolol

EXTRA EDGE

- **Beta-3 receptors** are located on **adipose tissue** and their stimulation causes **lipolysis**.

Types of α Receptors

	α1	α2
Location	Postjunctional on effector organs	Prejunctional on nerve endings, (α2A) also postjunctional in brain, pancreatic β cells, platelets and extrajunctional in certain blood vessels

Contd...

Contd...

	α1	α2
Functions	GU Smooth muscle—contraction Vasoconstriction Gland—secretion Gut—relaxation Heart—arrhythmia Liver—glycogenolysis	Inhibition of transmitter release Vasoconstriction ↓ central sympathetic flow ↓ insulin release Platelet aggregation
Selective agonist	Phenylephrine, methoxamine	Clonidine
Selective antagonist	Prazosin	Yohimbine, rauwolscine
Effector pathway	IP3/DAG ↓ Phospholipase A2 - ↓PG release	cAMP ↓ K+ channel ↓ IP3/DAG ↓

SYMPATHOMIMETICS

Drug	Selectivity	Indications
Direct sympathomimetics		
Epinephrine	α1, α2, β1, β2	Anaphylaxis, acute asthma, hypotension, shock, as a vasoconstrictor with local anesthetics
Norepinephrine	α1, α2, > β1	Hypotension (↓ renal perfusion)
Isoproterenol	β1 = β2	AV block (rare)
Dopamine	D1 = D2 > β > α	Inotropic AND chronotropic ; Shock (renal perfusion, heart failure)
Dobutamine	β1 > β2	Inotropic but NOT chronotropic; Shock, CHF, cardiac stress testing
Phenylephrine	α1 > α2	Used as pure Mydriatic when cycloplegia NOT required (fundus exam), nasal decongestion, vasoconstriction, antagonizes hypotension of spinal anesthesia
Salbutamol (Albuterol), terbutaline	β2 > β1	Asthma; Tocolytic (not routinely used now)
Ritodrine	β2	Tocolytic

Contd...

Contd...

Drug	Selectivity	Indications
Indirect sympathomimetic		
Amphetamine	Indirect general agonist, releases stored catecholamines	Attention deficit hyperactivity disorder, ADHD , narcolepsy, obesity
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion, urinary incontinence
Cocaine	Indirect general agonist, uptake inhibitor	Vasoconstriction, local anesthesia

EXTRA EDGE

- **Clenbuterol** is a **beta 2-adrenergic agonist** - potent, long-lasting **bronchodilation**; it is **abused by athletes and body builders** for its ability to alter body composition by reducing body fat and increasing skeletal muscle mass.

Selective β2 Stimulants

- The drugs are **salbutamol/salmeterol, formoterol**.
- They cause **bronchodilatation, vasodilatation** and **uterine relaxation** without producing significant cardiac stimulation. β2 selectivity is only relative. **Salbutamol has the highest ratio of β2:β1 action (about 10 times)**. They are primarily used in **bronchial asthma**. Other uses are:
 - As a **tocolytic** (uterine relaxant to delay premature labor) - **Ritodrine** and **terbutaline**.
 - In **hyperkalemic periodic paralysis**: cause increased potassium uptake by muscles
- Most important **side effect** is **muscle tremor**.

Nasal Decongestants

- **Naphazoline, xylometazoline, oxymetazoline** are relatively selective **α2 agonists**, which on topical application as dilute solution produce local **vasoconstriction**.

Vasomotor Reversal of Dale

- Rapid IV injection of Adrenaline in animals produces a marked increase in systolic and diastolic BP. But when an alpha (α-1) blocker has been given previous to injection, **ONLY fall in BP** due to beta (β-2) mediated vasodilatation is seen. This is called '**vasomotor reversal of Dale**'.

α-Antiadrenergic Drugs (α-Blockers)

Drug	Indication	Toxicity
Nonselective		
Phenoxymethamine (irreversible) and phenolamine (reversible)	Pheochromocytoma (use phenoxymethamine before surgery since high levels of released catecholamines will not be able to overcome blockage)	Orthostatic hypotension, reflex tachycardia
Prazosin, terazosin, doxazosin, tamsulosin	Urinary retention in BPH, hypertension	1 st dose orthostatic hypotension, dizziness, headache; Tamsulosin causes IFIS (Intraoperative Flappy Iris Syndrome)
α-2 selective		
Mirtazapine	Depression	Sedation, ↑cholesterol, ↑appetite

β-Antiadrenergic Drugs (β-Blockers)

Nonselective (β1 and β2)	Cardioselective (β1)
Without intrinsic sympathomimetic activity (ISA) Propranolol, sotalol, nadolol, timolol	Metoprolol, Nebivolol, Celiprolol, Betaxolol, Atenolol, Bisoprolol, Esmolol (" MNC BABE!! ")
With ISA Pindolol	
With additional β blocking property Labetalol, Carvedilol (no ISA)	

Uses of β-Blockers

- **Hypertension** - ↓ cardiac output, ↓ rennin secretion
- **Angina pectoris** - ↓ heart rate and contractility, resulting in ↓ oxygen consumption
- **MI** - β-blockers ↓ mortality
- **SVT** (propranolol, esmolol) - ↓ AV conduction velocity (class II antiarrhythmic)
- **CHF** - slows progression of chronic failure
- **Glaucoma** (timolol, betaxolol) - ↓ aqueous humor production
- **Albuterol, ritodrine, terbutaline**, are **beta-2 agonists** useful in treatment of **asthma** and as **tocolytics**.
- **Side effects of beta blockers**: see under glaucoma in ophthalmology chapter (Pg 569).

Golden MCQ Points about Beta Blockers

- Carvedilol: **anti-oxidant** property
- Penbutolol and pindolol: approximately **100% bioavailability**
- Propranolol: **Inhibits peripheral conversion** of thyroxine to tri-iodo-thyronine; it is also used in treating **essential tremors**
- Sotalol: **blocks potassium channels** in the heart
- Tilisolol: **opens potassium channels** in the heart
- Bucindolol: **increases plasma HDL** but does not affect plasma triglycerides
- Esmolol: **Sharest acting** beta blocker; used IV only
- Nadolol: **Longest acting** beta blocker
- Beta blockers with **membrane stabilizing (local anesthetic)** activity: Propranolol, Pindolol, Alprenolol, Labetalol, Metoprolol (PALM)
- Nebivolol: **Nitric oxide releasing** Beta blocker (causes vasodilation, hence no impotence!)
- Beta blockers with **high protein binding**: Carvedilol (98%)> propranolol (90%)> penbutolol (88%)
- Lipid soluble** beta blockers: Carvedilol, Bisoprolol, Propranolol, Timolol

SKELETAL MUSCLE RELAXANTS

Peripherally Acting Muscle Relaxants

- This has been covered in detail in the *Anesthesia* chapter (Pg 1143).

Centrally Acting Muscle Relaxants (Spasmolytics)

- These drugs reduce skeletal muscle tone by a selective action in the cerebrospinal axis without altering consciousness
- Mephenesin group**: Carisoprodol; Chlorzoxazone; Chlormezanone; methocarbamol

- These drugs are spinal internuncial neuron blocking agents (at the level of brainstem); they preferentially inhibit polysynaptic reflexes without affecting monosynaptic (knee jerk) tendon reflexes
- BZD group**: Diazepam, Clonazepam
 - These inhibit both monosynaptic as well as polysynaptic reflexes; they enhance GABA-ergic transmission at all GABA synapses BUT their site of action in reducing spasticity is **supraspinal**
- GABA derivative**: Baclofen
 - Baclofen is an orally active GABA-mimetic drug which acts as GABA agonist at GABA-B receptors at **spinal** level; used to relieve painful spasticity in multiple sclerosis.
- Central Alpha-2 Agonist**: Tizanidine
 - Tizanidine has alpha-2 agonist action in the spinal cord and inhibits the release of excitatory amino acids in spinal interneurons. Used in treating spasticity in **multiple sclerosis and Amyotrophic lateral sclerosis**. (has very less effect on BP as compared to clonidine)
- Miscellaneous agents**: Tolperisone HCl
 - A centrally acting muscle relaxant with local anesthetic properties.

Directly Acting Muscle Relaxant - Dantrolene

- Reduces depolarisation induced release of Ca++ from sarcoplasmic reticulum**; hence interferes with excitation contraction coupling.
- It is the **DOC for malignant hyperthermia**; also used in neuroleptic malignant syndrome

Contd...

Receptor	Distribution and Action
H3	Presynaptic H3 receptors serve as feedback inhibitors for release of histamine In heart, H3 receptors on sympathetic nerve terminals decreases norepinephrine (NE) release and helps to prevent arrhythmias that may result from NE discharge during stress or ischemia
H4	Present in hematopoietic system (eosinophils, neutrophils, CD4 T cells) - chemotaxis of WBCs

Contd...

HISTAMINE

Histamine Receptors and Actions

Receptor	Distribution and Action
H1	Smooth muscle contractile (bronchi, intestine, uterus) Blood vessels: vasodilation and increased permeability Sensory nerve endings: mediate itching and pain
H2	Acid secretion in Gastric glands Positive chronotropic + Inotropic effect on heart

HISTAMINE, SEROTONIN, BRADYKININ

Histamine Related Drugs

H1 agonists

Metahistine: used to treat **vertigo** since it causes vasodilation and improves blood flow to labyrinth and brainstem

H1 Antagonists

Both the generations of H1 antihistamines are used to treat and prevent symptoms of allergic rhinitis and urticaria.

1st generation

- Highly Sedative: Dimenhydrinate; Diphenhydramine; Doxylamine; Hydroxyzine; Promethazine
- Moderately sedative: Pyrilamine; Cyproheptadine; Pheniramine; Clemastine
- Mild sedative: Chlorpheniramine; Meclizine; Cinnarazine; Triprolidine

2nd generation

- Do NOT cross BBB and hence least sedating; have longer duration of action
- Astemizole; fexofenadine; cetirizine; loratidine, desloratidine; levocetirizine; Ebastine, Olopatadine

H2 Antagonists

These are drugs used to **treat peptic ulcers** (Ranitidine, cimetidine, famotidine, nizatidine) and are discussed separately under GIT of this pharmacology chapter (Pg 338).

H3 related drugs

Tiprolisant: Inverse H3 receptor agonist; used in narcolepsy

Some Special Uses of H1 Antihistamines

- Motion sickness**: Dimenhydrinate, diphenhydramine, meclizine, cyclizine (due to antimuscarinic activity)
- Sleeping Aids**: Doxylamine, Pyrilamine.
- Anti-emetics**: Hydroxyzine, promethazine
- Cinnarazine**: Treatment of **vertigo**; it is also a **calcium channel blocker**.
- Desloratidine** has **anti-inflammatory effect** also
- Olopatadine eyedrops** used for **ocular itching** in allergic conjunctivitis
- Cyproheptadine has **anti-serotonin effects**.

EXTRA EDGE

- Astemizole and Terfenadine** when used with enzyme inhibitors like **ketacanazole, erythromycin, chloramphenicol** may cause **torsades de pointes**.
- Fexafenadine** is an active metabolite of terfenadine and does not cause torsades de pointes.

SEROTONIN

- Serotonin (5-Hydroxy Tryptamine, 5-HT)** is formed from the amino acid **tryptophan**.
- Structures rich in serotonin are **GIT enterochromaffin cells; platelets and lungs, bone marrow, pineal gland** (precursor of **melatonin**) and CNS (as neurotransmitter).

5-HT Receptors and Related Drugs

Receptor type and Functions	Agonist and use	Antagonist and use
5-HT1 and subtypes Cerebral vasoconstriction Affects mood and behavior	Buspirane (5-HT1A) - used as anti-anxiety drug Sumatriptan (5HT1D) - used for treating acute migraine	Ergatamine (5-HT 1A-1D) - used in migraine treatment
5-HT2 and subtypes Smooth muscle contraction Platelet aggregation	Lysergic acid diethylamide (LSD) - hallucinogen and drug of abuse-	Ketanserin (5-HT2A) - anti-hypertensive Cyproheptadine (5-HT2A) - was used for migraine prophylaxis, controlling GI manifestations of carcinoid, dumping syndrome Methysergide (5HT2A-2C) - was used for migraine prophylaxis Clozapine, Risperidone - newer antipsychotic agents (5HT2A-2C)
5-HT3 CNS - Excitation of nociceptive neurons in area postrema causes anxiety and emesis	2-methyl-5-HT	Ondansetron, Granisetron - used as antiemetics
5-HT4 CNS - Hippocampal excitation GIT - Increased motility	Metoclopramide (gastric hurrying agent) Cisapride (used to treat gastro-esophageal reflux) Tegaserod (to treat irritable bowel syndrome with constipation)	

BRADYKININ

- Bradykinin is derived by the action of plasma kallikrein on HMW kininogen.
- It is a potent vasodilator (10 times more than histamine)
- B2 receptor is responsible for majority of actions of bradykinin; it activates phospholipase C.

- *Icatibant* is a selective *bradykinin B 2 receptor antagonist* approved for treating *acute hereditary angioedema* in adults by SC injection.
- *Aprotinin* is a nonspecific *kallikrein antagonist* administered to patients undergoing *CABG* to *minimise bleeding*.

PROSTAGLANDINS AND LEUKOTRIENES

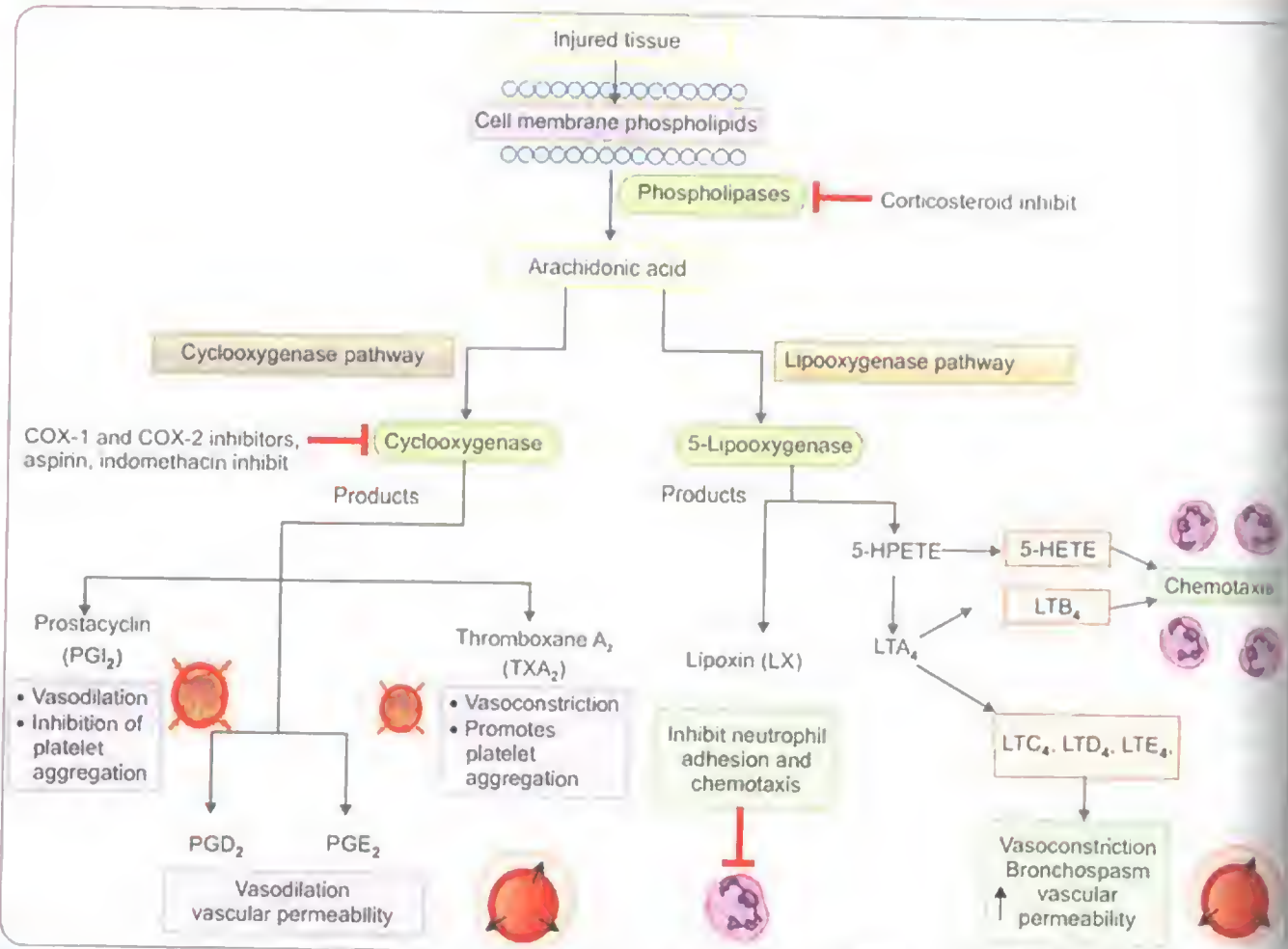


Fig. 9.1: Arachidonic acid metabolites involved in Inflammation. The cyclooxygenase pathway generates prostaglandins (PGIs) and thromboxane (TXA₂). The lipoxygenase pathway forms lipoxins (LXs) and leukotrienes (LTEs). Abbreviation: COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid

- Cell membrane injury releases membrane phospholipids which is converted to arachidonic acid by **Phospholipase A₂**.
- Arachidonic acid can be converted enzymatically to **prostaglandins and leukotrienes** - these arachidonic acid derivatives are called **eicosanoids**.
- Either of the enzymes **cyclo-oxygenase (COX)** or **lipoxygenase (LOX)** may act on arachidonic acid

Cyclo-Oxygenase	Lipo-Oxygenase
• COX pathway yields Prostaglandins (PG) and thromboxane A₂ (TXA₂) .	• LOX pathway operates mainly in the lung, WBC and platelets .

Contd

Cyclo-Oxygenase	Lipo-Oxygenase
• Two isoenzymes - COX-1 and COX-2.	• LOX pathway yields Leukotrienes and Lipoxins .
• COX-1 is constitutively expressed (i.e, it is normally present in most cells); it has physiological ('house-keeping') functions such as secretion of mucus for protection of gastric mucosa, hemostasis and maintenance of renal functions.	• 5-HETE (HydroxyEicosaTetraEnoic acid) is the precursor of leukotrienes.
• COX-2 is inducible in Inflammatory cells by an inflammatory stimulus (endotoxins, cytokines); it lead to inflammatory changes.	

- *Non selective NSAIDs* (Aspirin, ibuprofen, and naproxen) inhibit both COX1 and COX2 (can cause gastritis).
- Hence *selective COX-2 inhibitors* (celecoxib) are now available as NSAIDs to counter gastritis side effects.
- *Zileuton* is a 5-lipoxygenase inhibitor - prevents leukotriene synthesis. Used in asthma; limited duration of action; hepatotoxic.
- *Zafirlukast* (Montelukast, Pranlukast, Irelukast) are leukotriene L₁ receptor antagonists. Used in prophylaxis of asthma.
- See more below under the topic NSAIDs.

Role in Acute Inflammation

Prostaglandins	
Thromboxane A₂ (TXA₂)	Vasoconstriction (↑ vascular tone) Promotes platelet aggregation ("ThromBOXane = platelets are BOXed in") Bronchoconstriction
Prostacyclins (PGI₂)	Vasodilator (↓ vascular tone) Inhibits platelet aggregation ("PGI ₂ = Platelet-Gathering Inhibitor") ↓ tone of bronchi and uterus (PGI ₂ = Power-Gaining Inhibitor) (all ↓ tone!!)
PGE₂	Vasodilator (↓ vascular tone) Bronchodilator (↓ bronchial tone) ↑ vascular permeability ↑ uterine tone (contraction) of pregnant uterus Inhibition of gastric acid secretion and stimulates gastric mucus secretion Causes cytokine induced fever during infections; also PGE₂ is increased in hypothalamus during fever

Prostaglandins	
PGF_{2α}	↓ Intraocular pressure Vasoconstrictor
PGD₂	Vasodilation ↑ vascular permeability Chemo-attractant for neutrophils
Leukotrienes	
Leukotrienes (LTC₄ and LTD₄)	SRS-A (Slow Reacting substance of Anaphylaxis) is LTC ₄ and LTD ₄ ↑ vascular tone, (vasoconstriction) ↑ bronchial tone (bronchospasm) ↑ vascular permeability
LTA₄ and LTB₄	↑ neutrophil chemotaxis Release of lysosomal enzymes
Lipoxins	Inhibit neutrophil chemotaxis and leukocyte adhesion

Clinical Uses of Prostaglandins

- Induction/augmentation of **labor; cervical priming, control of PPH** (Dinoprostone, PGE₂)
- **Abortion:**
 - First trimester (Misoprostol, PGE₁);
 - Second trimester (Dinoprostone, PGE₂ vaginally) or carboprost, PGF_{2α} (intra-amniotic)
- **Peptic ulcer** healing (misoprostol, PGE₁; Enoprostil PGE₂).
- **To prevent platelet aggregation** in extra-corporeal circulation like renal dialysis and cardio-pulmonary bypass (Epoprostenol, PGI₂)
- To **treat pulmonary HTN** (Epoprostenol, PGI₂; Treprostinil, PGI₂)
- For **patency of PDA** (Alprostadil, PGE₁; Epoprostenol, PGI₂)
- **Reduction of IOP** in glaucoma (PGF_{2α} derivatives - latanoprost, travoprost, bimatoprost and unoprostone)
- To treat **peripheral vascular disease** (Beraprost, PGI₂)
- Male **impotence** (Alprostadil, PGE₁)
- To **reduce infarct size** in immediate post MI period (Iloprost, PGI₂)

EXTRA EDGE

- A **new iso-enzyme COX-3** has been identified in cerebral cortex and heart. It is involved in **pain perception and fever** BUT not in inflammation; It is selectively inhibited by **paracetamol**.
- The term **Prostanoids** = PG + TXA₂

NSAIDs, DRUGS FOR GOUT AND RHEUMATOID ARTHRITIS

Classification of NSAIDs

- **NON-selective Irreversible COX inhibitors (COX1 > COX2):** Aspirin (acetyl salicylic acid); sodium salicylate; sulfasalazine, olsalazine, methysalicylate
- **NON-selective Reversible COX Inhibitors (COX1 + COX2):** Indomethacin, Oxyphenbutazone; Ibuprofen, ketoprofen, Flurbiprofen, Naproxen, Mefenamic acid, Tenoxicam, Piroxicam, Ketorolac, Tolmetin, Oxaprozin, Diflunisal, Diclofenac, Aceclofenac
- **Weak inhibitors of COX2 > COX1:** Nimesulide (15 times more COX2 selective; has other modes of anti-inflammatory action also).
- **Preferential COX2 inhibitors (COX2 > COX1, 20 times!):** Meloxicam, Etoricoxib; Nabumetone
- **Selective COX2 Inhibitors (50 times COX2 selective!):** Rofecoxib, Celecoxib, Valdecoxib, Etoricoxib, Parecoxib
- **COX 3 Inhibitor:** Paracetamol
- **NSAIDs which do NOT inhibit prostaglandin synthesis:** Nefopam, Diacerein.
- NSAID = Non Steroidal Anti Inflammatory Drugs

Aspirin: Prototype NSAID - Effects and Uses

- **Analgesia** - used for headache, myalgia, neuralgia, toothache, dysmenorrhea, arthritis etc.
- **Antipyretic** - Reduces fever.
- **Anti-inflammatory** - in osteo and rheumatoid arthritis and rheumatic fever.
- **Inhibits platelet aggregation:** Post MI to reduce risk of reinfarction; treatment of TIA; prophylaxis of DVT.
- **Dysmenorrhea:** Aspirin reduces uterine prostaglandin levels and helps in relief.
- **Pre-eclampsia:** suppresses TXA2 production.
- **Low dose aspirin** beneficial in prevention of **colonic cancer and Alzheimer's dementia**.

Adverse effects of Aspirin

- GI mucosal damage; **gastritis**, hemorrhage, ulceration.
- Increase in bleeding tendency: **Stop aspirin 1 week before surgery**.
- Toxicity: Initially **respiratory alkalosis (lead to salicylism)** - headache, vertigo, tinnitus, hyperventilation, vomiting); then **respiratory acidosis** and with increasing doses **metabolic acidosis** results.
- Effect on uric acid excretion: At low doses it decreases uric acid excretion; at high doses (> 5 g/day) it is **uricosuric**.
- **Reye's syndrome:** If aspirin is given for treating children < 12 years of age; liver damage and encephalopathy can occur when recovering from febrile viral infection.

MCQ points about other NSAIDs

- **Methylsalicylate:** A.k.a 'oil of wintergreen' for external use only in pain balms (Iodex).
- **Salicylic Acid:** **keratolytic** agent - for local treatment of corns.
- **Sulfasalazine:** is converted to 5-ASA (aminosalicylic acid) by bacteria in colon; used in treatment of **ulcerative colitis** (also **olsalazine**).
- **Diflunisal:** seldom used; does NOT cross BBB - no antipyretic action.
- **Indomethacin:** Indole derivative; preferred in **ankylosing spondylitis**; contraindicated in pregnancy.
- **Oxyphenbutazone:** **obsolete**.
- **Ibuprofen:** **hypersensitivity** risk.
- **Flurbiprofen:** topical **eyedrops** also available
- **Diclofenac and aceclofenac:** almost **99% protein bound**; NOT suitable for IV use.
- **Mefenamic acid:** very effective in **dysmenorrhea**.
- **Ketorolac:** used as **eyedrops** for allergic conjunctivitis
- **Piroxicam and tenoxicam:** long acting; long half life once daily usage.
- **Nimesulide:** **Other MOA** implicated are reduced superoxide generation; free radical scavenging action; inhibition of PAF synthesis.
- **Coxibs:** Highly selective **COX2 inhibitors**; **less GI side effects and NO impact on platelet aggregation** (**Rofecoxib** was **withdrawn** due to increased **cardiac mortality** - acute MI and stroke).
- Atypical NSAIDs: Nefopam and Diacerein

Paracetamol (Acetaminophen) Poisoning

- **Major pathway:** Normally paracetamol is metabolised by **glucuronide and sulfate conjugation**.
- **Minor pathway:** A small proportion of paracetamol is metabolized by cytochrome P450 **CYP2E1** to yield N-acetyl-p-benzoquinone-imine (NAPQI) - a toxic metabolite. This **NAPQI** is detoxified by binding to glutathione to become harmless, water-soluble **mercapturic acid**, which undergoes renal excretion.
- With toxic doses of paracetamol (4-5 g/day), large amounts of NAPQI are formed which cannot be handled by glutathione. This NAPQI accumulated and causes necrosis in liver (**centrilobular necrosis**) and kidneys.
- The chances of possible, probable, and high-risk hepatotoxicity can be derived from a **nomogram** plot.
- Treatment should started early (within 30 minutes upto 16 hours)
- Gastric lavage; oral activated charcoal.
- **Drug of choice:** **IV N-acetylcysteine**; oral **methionine** can also be used.

DRUGS FOR GOUT

Drugs Used in Acute Gout

- **Drugs which inhibit Neutrophil migration into joints:** Colchicine
- **Drugs which inhibit pain and inflammation:** NSAIDs, prednisolone

Drugs Used in Chronic Gout

- **Uric acid synthesis (Xanthine oxidase) inhibitors:** Allopurinol; Febuxostat
- **Uricosuric drugs:** Probenecid; sulfinpyrazone; Benzbromarone
- **Uricase-mimetic agents:** Pegloticase

MCQ points about above drugs

- Colchicine treated neutrophils develop a 'drunken walk' and are prevented from migrating into joints.
- Diarrhea is a prominent side effect of Colchicine.
- Other (non-gout) uses of Colchicine: Pseudogout; Familial Mediterranean fever; Recurrent Pericarditis; Amyloidosis, Scleroderma and Cirrhosis.
- Febuxostat is a more potent and selective inhibitor of xanthine oxidase compared to allopurinol.

DRUGS FOR RHEUMATOID ARTHRITIS

- **NSAIDs:** Traditional NSAIDs and COX-2 inhibitors (rofecoxib etc).
- **Corticosteroids:** Low-dose corticosteroids often are used as a "bridge" to reduce disease activity until the slower acting DMARDs take effect.

CARDIOVASCULAR SYSTEM

DIGOXIN

- **Mechanism of action:** Direct **inhibition of Na⁺/K⁺ ATPase** leads to indirect inhibition of Na⁺/Ca²⁺ exchanger/antiport. **Increased intracellular Ca²⁺** → positive inotropic action → increase stroke volume and cardiac output; stimulates vagus nerve
- **Clinical use:** **CHF** (↑ contractility); **Atrial fibrillation** (↓ conduction at AV node and depression of SA node); **Atrial tachycardia**.
- **Pharmacokinetics:** Digoxin -75% bioavailability; 20-40% protein bound; **t_{1/2} = 40 hours**; **renal excretion**;
- **Digoxin safe in liver disease** (since renal excretion, hence dose reduced in renal failure); **Digitoxin** dose should be **reduced in liver failure**.

Disease Modifying Anti Rheumatoid Drugs (DMARDs)

Synthetic DMARDs

- **Methotrexate** (**First choice**, Sfx - **pancytopenia, hepatotoxicity**)
- **Sulfasalazine** (Sfx—hemolysis in **G-6-PD deficiency**)
- **Leflunomide** (**pyrimidine synthesis inhibitor**)
- **Hydroxychloroquine** (**bull's eye maculopathy**)
- **Tofacitinib** (inhibitor of **Janus kinase-3**; risk of **TB reactivation**!)

Biologic DMARDs

- **TNF-alpha inhibitors:** **Etanercept, infliximab, adalimumab, golimumab, and certalizumab pegal** (contraindicated in CHF and can cause increased leukemia and malignancy).
- **Abatacept**, a recombinant protein made by fusing a fragment of the Fc domain of human IgG with the extracellular domain of a T-cell inhibitory receptor (CTLA4), blocks T-cell co-stimulation.
- **Rituximab anti-CD20** antibody that depletes B cells
- **Tocilizumab** is a monoclonal antibody that blocks the receptor for **IL-6**.
- **Anakinra: IL-1 receptor antagonist**; should NOT be combined with an anti-TNF drug due to the high rate of serious infections [Anakinra is also used in autoinflammatory/inflammasome syndromes - see **Immunology** chapter for examples of inflammasome (Pg 308)].

Digoxin Toxicity and Treatment

- **Toxicity worsened by** Renal failure (↓ excretion); Quinidine, propafenone, amiodarone; CCBs (verapamil, diltiazem); Diuretics
- **Precipitated by** hypokalemia, hypercalcemia, hypomagnesemia, hypo/hypothyroidism
- **Clinically:** Nausea, vomiting, diarrhea, blurry vision, **yellow vision**; also **gynecomastia**
- **ECG:** ↑ PR, ↓ QT, scooping T wave inversion, arrhythmia (esp. **paroxysmal atrial tachycardia**), hyperkalemia.
- **Antidote:** Anti-dig **Fab fragments**, **lidocaine**, slowly **normalize K⁺, Mg²⁺**

NITRATES

- Nitrates cause direct **nonspecific smooth muscle relaxation** (veins > arteries)

- Cause both preload as well as afterload reduction → ↓ cardiac work and oxygen consumption. They favor redistribution of coronary flow to ischemic areas in angina patients.
- They dilate *cutaneous vessels* (esp. over face which leads to flushing) and *meningeal vessels* (cause throbbing headache). Splanchnic and renal blood flow are ↓.
- **Longest acting nitrate** = *Penta ethyl trinitrate*
- **Shortest acting nitrate** = *glyceryl trinitrate*
- MOA of nitrates: Nitrates get denitrated in smooth muscle to release **nitric oxide** → activates **guanylyl cyclase** → activates **cGMP** → **relaxation** occurs. (Even during **erection**, same mechanism of nitric oxide occurs).
- All nitrates undergo extensive first pass metabolism **except isosorbide mononitrate**.
- Tolerance to nitrates occurs if they are present continuously in the body; this tolerance wears off rapidly (within hours) when the body is free of the drug.
- *Sildenafil (Viagra)* causes **dangerous potentiation of nitrate action**: severe hypotension, MI and deaths have occurred.

ANTIHYPERTENSIVES

Class of Medication and Examples	Side Effects/Caution	Mechanism of Action
Diuretics		
Thiazides (Hydrochlorothiazide, Chlorthalidone)	Hyperglycemia, Hypercholesterolemia/ Hypertriglyceridemia, hypercalcemia; hyperuricemia/ gout; HYPO kalemia	Reduce circulatory volume to decrease Cardiac Output (CO) and mean arterial pressure; In long term they reduce peripheral vascular resistance
Aldosterone receptor blockers, K⁺-sparing (spironolactone, amiloride, eplerenone)	Hyperkalemia, metabolic acidosis, gynecomastia .	
Loop diuretics (frusemide, torsemide, bumetanide, ethacrynic acid)	SE same as thiazides; too potent for regular use (higher risk of excessive diuresis and electrolyte imbalance); ototoxicity	
Beta-Blockers		
Nonselective (propranolol, timolol)	Asthma, bronchoconstriction (if nonselective), 2 nd or 3 rd degree heart block , HDL reduction, ↑ triglycerides	Decrease HR, contractility, CO, and decrease renin secretion to decrease total peripheral resistance
Beta 1-selective/cardi selective (metoprolol, atenolol, esmolol)		
Calcium Channel Blockers		
Nondihydropyridines (diltiazem, verapamil)	Ankle edema, headache, bradycardia, increased GI reflux, dizziness, AV block, urinary frequency, constipation, CHF due to cardiac depression (MC with verapamil)	Reduce influx of calcium during cardiac and vascular smooth muscle contraction to cause vasodilation
Dihydropyridines (nifedipine, amlodipine, felodipine)		

BETA BLOCKERS

See under pharmacology chapter (Pg 323).

CALCIUM CHANNEL BLOCKERS

- There are three types of CCBs—L-type, T-type and N-type
- Only the **voltage sensitive L-type channels** are blocked by CCBs.
- Clinical uses:
 - **Prinzmetal** angina: DOC is **nifedipine** > diltiazem > verapamil.
 - In arrhythmia: verapamil > diltiazem
 - In **hypertension**: nifedipine and diltiazem > verapamil
 - CCB with predominant **peripheral action** (maximum Smooth muscle relaxation): nifedipine (used as tocolytic!)
 - **Nimodipine** used in **subarachnoid hemorrhage**.
 - **Side effects**: **Ankle edema** with **nifedipine** **Constipation** with **verapamil**.

Class of Medication and Examples	Side Effects/Caution	Mechanism of Action
Angiotensin Converting Enzyme – Inhibitors (ACEIs)		
" prils " (lisinopril, captopril, enalapril, lisinopril, quinopril, ramipril, perindopril, trandolapril, moexipril (NO prodrugs for lisinopril and captopril))	Dry Cough, Angioedema , rarely, Proteinuria , Taste alteration and rash (MC with captopril), hypotension , Pregnancy (CI due to teratogenicity), Renal dysfunction (azotemia), hyperkalemia (Increased K ⁺); CI in and bilateral renal artery stenosis "CAPTOPRIL"	Block conversion of angiotensin I to angiotensin II and increase circulating bradykinin to decrease angiotensin II vasopressor activity and aldosterone secretion causing decrease in total peripheral resistance
Angiotensin 2 receptor blockers (ARBs)		
losartan, Losartan, Valsartan,坎andesartan	Major advantage is NO cough , Rest Side effects as in ACE inhibitors above; higher cost;	Block binding of angiotensin II to receptors to inhibit vasopressor activity and decrease aldosterone secretion
Renin Inhibitors		
Aliskiren	Angioedema, hypotension, hyperkalemia; CI in pregnancy	Binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen, rate-limiting step in the renin-angiotensin cascade
Alpha-blockers		
Non-selective phenoxybenzamine selective prazosin, doxazosin, terazosin	Syncope with first dose; postural hypotension , dizziness, palpitations, headache, weakness, drowsiness, sexual dysfunction, anticholinergic effects, urinary incontinence; first-dose effects may be less with doxazosin. Also useful for relief of prostatism . Phenoxybenzamine indicated in pheochromocytoma	Block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance.
Central sympatholytics		
clonidine, Methyldopa, Reserpine	Sedation, dry mouth , sexual dysfunction, headache, bradyarrhythmias, depression . Methyldopa also causes hepatitis, hemolytic anemia , fever. "Rebound" hypertension may occur even after gradual withdrawal.	Lower BP by stimulating α₂-adrenergic receptors in the central nervous system, thus reducing efferent peripheral sympathetic outflow
Direct vasodilators		
hydralazine	SLE-like syndrome , GI disturbances, reflex tachycardia, headache, nasal congestion, rash,	Direct relaxation of vascular smooth muscle
Minoxidil	Hirsutism , pericardial effusion, thrombocytopenia, reflex tachycardia, salt retention, angina, headache,	

EXTRA EDGE

- **Losartan** has additional PPAR gamma activating property and has shown promise as anti diabetic also hence called "metabolic sartan".
- **Losartan blocks thromboxane A2** receptor and has some platelet anti-aggregatory property.

Recommendations and Contraindications for Antihypertensive Drug Selection

Associated Condition	Recommended Antihypertensive	Recommended Reason	Contraindicated Antihypertensive	Contraindicated Reason
DM	ACE-I	Delays renal damage	Thiazide diuretic Beta-blocker	Impaired glucose tolerance Masks signs of hypoglycemia
CHF	ACE-I Diuretic	Lower mortality Lower mortality	Calcium channel blocker	Reduced rate/contractility may exacerbate CHF
Asthma/COPD			Nonselective beta-blocker	Exacerbates broncho-constriction
Post-MI	Beta-blocker ACE-I	Lower mortality Lower mortality		
BPH	Selective α_1 -blocker	Decrease symptoms		
Migraine headache	beta-blocker	May ↓ symptoms		
Osteoporosis	Thiazide diuretic	Maintains normal/↑ serum calcium		
Pregnancy			Thiazide diuretic ACE-I ARB	↑ blood volume during pregnancy should be maintained Teratogenic Teratogenic
Gout			Diuretic	↑ serum uric acid
Depression			Beta-blocker	May worsen symptoms

Pregnancy and Anti-hypertensives

Anti-hypertensive drugs to be AVOIDED during pregnancy

- **Diuretics:** Tend to reduce blood volume – accentuate uteroplacental perfusion deficit (of toxemia) – increase risk of fetal wastage, placental infarcts, miscarriage, stillbirth.
- **ACE inhibitors, AT1 antagonists:** risk of fetal damage, growth retardation
- **Nonselective beta-blockers:** propranolol implicated in causing LBW, decreased placental size, neonatal bradycardia and hypoglycemia.
- **Sod. Nitroprusside**

- Harrison, 19th/Pg 46 mentions "Alpha-Methyldopa, labetalol, and nifedipine are the MC used medications for the treatment of chronic hypertension in pregnancy."

Hypertensive Urgency and Emergencies

- **Systolic BP > 180 or diastolic BP > 120 mmHg** with evidence of active **end organ damage** is called '**Hypertensive emergency**' while the same elevation of BP without end organ damage is called '**hypertensive urgency**'

- Drugs used for treatment are:
 - **Sodium nitroprusside (DOC, most effective drug)**
 - **Glyceryl trinitrate** (esp. after MI, cardiac surgery, LVF, unstable angina)
 - Diazoxide (constant monitoring NOT reqd)
 - Hydralazine (esp. in eclampsia, AVOID in aortic dissection and MI)
 - Esmolol (short acting, USED IN aortic dissection)
 - Phentolamine (**DOC for hyperadrenergic episodes**)
 - HTN in pheochromocytoma, cheese reaction, clonidine withdrawal)
 - Labetalol
 - Furosemide (adjunct with any of the drugs above).

EXTRA EDGE

- Drugs which were used earlier but NOT NOW are:
 - Nifedipine, Capropril, Clonidine "NCC".

VASODILATORS

Drugs reducing Preload (Venodilators)

Glyceryl trinitrate
Isosorbide nitrate

Contd.

Contd.

Drugs reducing Afterload (Arteriolar dilators)

Hydralazine
Minoxidil
CCBs (nifedipine)
K⁺ channel openers (nicorandil)

Contd...

Contd...

Drugs reducing Both Pre- and Afterload (mixed-dilators)

ACE Inhibitors
AT1 antagonists (ARBs)
Prazosin (alpha 1 blocker)
Amrinone, milrinone
Nitroprusside

ANTIARRHYTHMIC MEDICATIONS

Class	Mechanism of Action	Examples	Potential Uses
I Membrane stabilizing agents (Na channel blockers)			
IA	↑ AP, ↑ QT interval, ↑ ERP	Quinidine, procainamide, disopyramide	PSVT, Afib, Aflutter, Vtach
IB	↓ AP	Lidocaine, mexiletine	Acute ventricular (post-MI Vtach) and digitalis induced arrhythmias
IC	No effect on AP	Flecainide, propafenone, moricizine	Intractable SVT, Vtachs that progress to VF
II	β-blockers	Propranolol, esmolol, metoprolol	PSVT and Afib
III	K ⁺ channel blockers ↑ AP and ↑ ERP	Amlodarone, sotalol, bretylium Dofetilide, Ibutilide	Afib, Aflutter, Vtach (not bretylium). Ibutilide is called pharmac. defibrillator
IV	Calcium-channel blockers	Verapamil, diltiazem	PSVT, MAT, Afib, Aflutter
Others	K channel activation, decrease in intracellular cAMP	Adenosine	PSVT (DOC is adenosine)

Key: AP, action potential; Afib, atrial fibrillation; Aflutter, atrial flutter; cAMP, cyclic adenosine monophosphate; K, potassium; ERP, effective refractory period; MAT, multifocal atrial tachycardia; Na, sodium; PSVT, paroxysmal supraventricular tachycardia; Vtach, ventricular tachycardia.

EXTRA EDGE

- Most antiarrhythmics are pregnancy **category C EXCEPT Amiodarone** which is a pregnancy "category D" drug. (phenytoin and atenolol, though not commonly used are also category D).
- **Treatment of CHF** including **newer drugs like sacubitril and ivadabine** are mentioned in the CVS part in **medicine** chapter (Pg 760).

Important Antiarrhythmic Side Effects

- **Amiodarone toxicity:** pulmonary fibrosis, corneal deposits, hepatotoxicity, skin deposits, photodermatitis, CNS effects, constipation, CVS (bradycardia, heart block, CHB), **hypothyroidism, hyperthyroidism**.
- **Quinidine:** **Cinchonism** —headache, tinnitus, **thrombocytopenia**, torsades de pointes, ↑ QT interval.
- **Procainamide:** reversible **SLE like** syndrome.
- **Adenosine:** cough, flushing
- **Sotalol:** bronchospasm (**beta-blocker effect**)

DRUGS FOR DYSLIPIDEMIA (LIPID LOWERING DRUGS)

Drug	MOA	Side Effects	Major Indications
HMG-CoA reductase inhibitors - Statins (Atorva, prava; simva; atorva; rosuv; pitava; statins)	Inhibit cholesterol precursor mevalonate SOA: Liver	Myalgia , Myositis, rhabdomyolysis , arthralgia, reversible hepatitis (elevated transaminases), dyspepsia	Elevated LDL-C Increased CV risk
Cholesterol absorption inhibitors (Ezetimibe)	Prevent cholesterol reabsorption at small intestinal brush border SOA: Intestines	Reversible hepatitis (elevated transaminases)	Elevated LDL-C

Contd...

Contd...

Drug	MOA	Side Effects	Major Indications
Fibrates (gemfibrozil, fenofibrate, bezafibrate)	Lipoprotein Lipase activators (PPAR alpha activators); Increased Lipoprotein lipase levels and decreased VLDL SOA: Blood	Dyspepsia, myalgia, gall/stones, elevated transaminases	Elevated Triglycerides
Bile acid sequestrants/resins (cholestyramine, colestipol, colesevelam)	Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more SOA: GI tract	Patients cannot tolerate bad taste, GI upset, ↓ absorption of fat soluble vitamins, exacerbation of hemorrhoids	Elevated LDL-C
Niacin (Nicotinic Acid)	Inhibits lipolysis in adipose tissue; reduces hepatic VLDL into circulation SOA: Liver	Facial flushing (↓ with aspirin), nausea, paresthesias, pruritus , ↑ LFTs, hyperuricemia (gout), insulin resistance (may precipitate diabetes)	Elevated LDL-C Elevated TG
MTP Inhibitor Lomitapide	Microsomal Triglyceride transfer Protein (MTP) inhibitor: Decreased VLDL production	Nausea, diarrhea, increased hepatic fat	HoFH (Homozygous familial Hyper-cholesterolemia)
ApoB inhibitor Mipomersen	Decreased VLDL production	Injection site reactions, flu-like symptoms, increased hepatic fat	HoFH (Homozygous familial Hyper-cholesterolemia)
PCSK9 Inhibitors Evolocumab, Alirocumab	Proprotein Convertase Subtilisin/Kexin type 9 inhibitors	No major adverse effects (drug used by SC injection every 2-4 weeks)	Heterozygous familial hyper-cholesterolemia

More About Statins

- Statins are the **most powerful drugs** which cause dose related **reduction in LDL** levels.
- Potency of statins** refers to their ability to **lower LDL-C** levels: **Rosuvastatin** is **MOST potent** statin.
- Pitavastatin** has **highest bioavailability**.
- Half life of statins is generally 1-3 hours except these 3 drugs: **Rosuvastatin (19 hours)** > **Atorvastatin (17 hours)** > **Pitavastatin (12 hours)** "**RAP**", hence these long acting statins can be taken **at any time of the day** BUT other statins must be taken **at bedtime** since HMG CoA reductase activity is highest in the night.

- Pravastatin** is **NOT** metabolized by cytochrome P450 pathway.
- All these statins are **FDA approved for children >10 years** EXCEPT **Pravastatin** which is approved for **>8 years**.

EXTRA EDGE

- Mipomersen** is an **antisense oligonucleotide**.
- Human monoclonal antibodies** used in treatment of hyperlipidemias are **evolocumab and alirocumab**.
- Gugulipid and Fish oil derivatives (Omega-3 fatty acids)** are used in prophylaxis of hyperlipidemias.

RESPIRATORY SYSTEM

DRUGS FOR ASTHMA

Drug	Mechanism of Action	Uses
RELIEVER THERAPIES (rapid relief of symptoms by bronchodilation)		
Inhaled Beta-2 Agonists		
Inhaled Short/Rapid-Acting Beta2 Agonists - SABA (salbutamol / albuterol, pirbuterol, levalbuterol, bitoloterol, terbutaline)	Branchodilators that relax bronchial smooth muscle; have rapid onset of action	First-line therapy used as and when required for mild intermittent cases and during acute exacerbations

Contd

Contd

Drug	Mechanism of Action	Uses
Inhaled Long-Acting Beta2 Agonists - LABA (salmeterol, formoterol, indacaterol)	Bronchodilators that relax bronchial smooth muscle; have gradual onset and sustained activity	Regular prophylaxis in patients with moderate persistent or severe asthma LABAs should NOT be used alone in the treatment of asthma as they do not control underlying inflammation and should be combined with Inhaled corticosteroids (ICS) . Hence fixed combination inhalers of LABA + ICS are available.
Inhaled Anticholinergics		
Tiotropium, Tiotropium bromide	Bronchodilator , BUT it is less effective than beta2-agonists in asthma therapy because it inhibit only the cholinergic reflex component of bronchoconstriction, whereas beta2-agonists prevent all bronchoconstrictor mechanisms.	It may be used only as an additional branchodilator in patients with asthma that is not controlled by ICS and LABA combinations.
Methylxanthines		
Theophylline	Branchodilator – by inhibiting phosphodiesterase , thereby increasing cAMP levels	Was widely prescribed as an oral (sustained release capsules) bronchodilator, especially because it was inexpensive . It has now fallen out of favor because side effects are common. IV aminophylline (a soluble salt of theophylline) was used for the treatment of severe asthma but has now been largely replaced by high doses of inhaled SABA.

CONTROLLER THERAPIES (Inhibit underlying inflammatory process)

Inhaled Corticosteroids (ICS)		
Beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Anti-inflammatory: Inhibit synthesis of virtually all cytokines . Inactivate NF-κB the transcription factor that induces the production of TNF-α	Preferred first line agents for all patients of all ages for persistent asthma Most effective controllers. Once or twice daily dosing only necessary.
Systemic Corticosteroids		
Hydrocortisone, prednisolone, methylprednisolone	Anti-inflammatory	Used IV or oral in acute exacerbations of asthma
Mast cell stabilisers		
Cromolyn sodium, Nedocromil sodium	Stabilizes mast cells and recruitment of eosinophils	Effective in allergen or exercise induced asthma; Rarely used now since 4 times daily inhaled dosage required (due to short duration of action)
Leukotriene receptor antagonists		
Montelukast, Zafirlukast	Block activity/production of leukotrienes that are involved in inflammation and bronchospasm	Oral agents; adjunctive therapy in mild persistent or worse cases; especially good for aspirin induced asthma
5-lipoxygenase inhibitor		
Zileuton	5-lipoxygenase inhibitor that decreases leukotriene production	Oral agents; adjunctive therapy in mild persistent or worse cases

Contd..

Contd...

Drug	Mechanism of Action	Uses
Immunomodulators		
Omalizumab	Monoclonal anti IgE antibody	SC use in children 12 years or older (18 years for reslizumab) for moderate to severe persistent allergic asthma
Reslizumab	Monoclonal anti-IL-5 antibody	For IV infusion only in moderate to severe persistent allergic asthma

More MCQ points Theophylline

- Theophylline is **metabolized by CYP450 in the liver**, and thus, plasma concentrations may be elevated by drugs that block CYP450 such as **erythromycin and allopurinol**. Other drugs may also reduce clearance by other mechanisms leading to increased plasma concentrations
- Serum concentrations of theophylline need to be monitored due to its **narrow therapeutic range**.
- **Increased clearance of theophylline** occurs with: Enzyme induction (rifampin, phenobarbitone, ethanol); Smoking tobacco, marijuana; High protein low carbohydrate diet; Barbecues meat childhood
- **Decreased theophylline clearance** occurs with: enzyme inhibition, CHF, Liver disease, Pneumonia, High protein diet, viral infection, old age

EXTRA EDGE

- **Adverse effect of nebulized salbutamol in hypoxic children:** Bronchospasm causes alveolar hypoxia which causes pulmonary vasoconstriction. This protective reflex phenomenon diverts blood to the better ventilated parts of the lung thus maintaining the ventilation perfusion ratio. Salbutamol prevents this beneficial reflex phenomenon by inhibiting the hypoxia induced pulmonary vasoconstriction resulting in pulmonary vasodilation. The latter leads to increased blood flow to the hypoxic alveolus (increased dead space ventilation!) aggravating the ventilation perfusion mismatch worsening hypoxia in the already compromised child. So it is not uncommon for a hypoxic child to deteriorate during salbutamol nebuliser therapy! hence high flow oxygen is given in hypoxic children to maintain oxygen saturation > 92%.

DRUGS FOR TUBERCULOSIS

First Line Anti TB Drugs

Drug	Mechanism of Action	Side effects	Remarks
Isoniazid (INH)	Inhibits mycolic acid cell wall synthesis via oxygen-dependent pathways. INH resistance is a/w ↓ catalase and peroxidase activity in the bacterium.	Peripheral neuritis (MC in slow acetylators) and Neurotoxicity (seizures); Hepatitis, optic neuritis, hemolysis in G6PD deficiency, SLE like syndrome	Bactericidal to both extra- and intra-cellular organisms. Pyridoxine , 10 mg orally daily as prophylaxis for neuritis. ("INH is Neurotoxic and Hepatotoxic ")
Rifampicin (R)	Blocks RNA synthesis by inhibiting DNA dependent RNA polymerase	Hepatotoxicity and P-450 drug interactions; orange colored urine and sweat (harmless); ' respiratory ' and ' abdominal ' syn.	Bactericidal to all subpopulations of TB bacilli, but acts best on intermittently dividing bacilli (spurters)
Pyrazinamide (P)	Derivative of Isonicotinic acid; inhibits mycolic acid synthesis but by interacting with a different fatty acid synthase encoding gene. More active at pH<6; good penetration into CSF	Hepatotoxicity (less in Indians) and hyperuricemia/gout	Bactericidal to slowly dividing intracellular bacilli and those within caseous granuloma (acidic pH at these sites)
Ethambutol (E)	Inhibits arabinosyl transferases involved in arabinoglycan synthesis and interferes with mycolic acid incorporation into mycobacterial cell wall	Optic neuritis, color vision disturbance (red green) - difficult to detect in children; hence avoid ethambutol in children . " Ethambutol affects Eyes "; peripheral sensory neuropathy ;	Bacteriostatic ; Fast multiplying bacilli are more susceptible as are many atypical mycobacteria. least potent of the first line drugs. (" StEth: Static -Ethambutol ")"

First Line Supplemental Anti TB Drugs

Streptomycin

- **Bind to 30S ribosomal subunit**; freeze initiation of protein synthesis and cause misreading of the mRNA code
- **Ototoxicity and Nephrotoxicity**; Bactericidal to extracellular bacilli only

Rifabutin

- Rifabutin, a semisynthetic derivative of rifamycin S, **inhibits mycobacterial DNA-dependent RNA polymerase**
- **Is recommended in place of rifampin for the treatment of HIV-co-infected individuals.**
- **SE:** can cause **uveitis, Cl difficile diarrhea, pseudo-typhoid** colored skin.

Rifapentine

- Similar to rifabutin.

Second Line Anti TB Drugs

Quinolones

- **Ciprofloxacin, Ofloxacin, Moxifloxacin** and **sparfloxacin** are active against *M. tuberculosis*, *M. avium* complex (MAC) and *M. fortuitum*. they penetrate cells and kill bacilli lodged in macrophages also. Included commonly in MAC regimens and against Multidrug resistant (MDR) TB.
- **SE:** rare SE are seizures, skin vasculitis, interstitial nephritis, acute renal failure.

Chlronamide

- Like INH, this is also a derivative of isonicotinic acid. **Bacteriostatic** against TB bacilli and some atypical mycobacteria. Most useful in **multidrug resistant TB**.
- **SE:** GI upset, hepatitis, mental disturbance, hypothyroidism, optic neuritis.

Capreomycin

- A **polypeptide** antibiotic; SE: Ototoxicity, nephrotoxicity.

Amikacin and Kanamycin

- These **aminoglycosides** are bactericidal to extracellular organisms. Kanamycin is not used because of its toxicity.
- Amikacin is active against *M. tuberculosis*, *M. scrofulaceum*, rapid growers, *M. avium* intracellulare and *M. leprae*.

Cycloserine

- A chemical analogue of **D-alanine**. Tuberculostatic and **also active** against some gram-positive bacteria, *C. coli* and chlamydia also.

- **SE:** **CNS toxicity** (psychosis, suicide, seizures, peripheral neuropathy, headache); pyridoxine 100 mg/day has to be used for preventing this.

Para-amino salicylic acid (PAS)

- PAS inhibits the growth of *M. tuberculosis* by impairing folate synthesis. It is **tuberculostatic**; one of the least active and only delays the development of resistance.
- **SE:** Epigastric pain, **goitre**, rashes, liver dysfunction.

Other Drugs

- Below drugs are referred to by WHO as "group 5" whose efficacy is not clearly defined are used in the treatment of patients with TB resistant to most of the first- and second-line agents.

Thiacetazone (Amithiozone)

- Widely used in **developing countries (low cost)** as a single-tablet combination with INH to prevent resistance to INH.
- Used very rarely in developed countries because it has been associated with severe and at times fatal skin reactions among HIV-infected patients.
- **SE:** hepatitis, exfoliative dermatitis, Stevens-Johnson syn. It is **not to be used by HIV infected patients** because incidence of serious toxicity (skin, GI) is higher.

Macrolides (Clarithromycin, Azithromycin)

- These are active against most nontubercular mycobacteria including MAC (most active against MAC and one of these drugs is an essential component of any regimen used for this purpose), *M. fortuitum*, *M. kansasii*, *M. marinum*.

Linezolid

- Linezolid is one of a new class of gram-positive-active anti- microbial agents called **oxazolidinones** that **inhibit protein synthesis** by binding to the **70S ribosomal initiation complex**.
- It is available in **IV and oral forms**.
- **Side effects** = **bone marrow suppression** (which appears to be dose dependent and reversible) and **peripheral neuropathy** (which appears to be neither dose dependent nor reversible).

Carbapenems

- Imipenem/cilastatin and meropenem.

Newer Anti TB Drugs

- The diarylquinoline **bedaquiline** and the nitroimidazole **delamanid**—have recently been approved for use in severe cases of MDR-TB.
- Bedaquiline has been approved **under the RNTCP** in Jan 2016.
- Bedaquiline blocks ATP synthase within mycobacteria.

GASTROINTESTINAL SYSTEM

DRUGS FOR PEPTIC ULCERS

Reduction of Gastric Acid Secretion

PPIs (proton pump inhibitors)

- Drugs: Omeprazole, Pantoprazole, Rabiprazole, Esomeprazole, Dexlansoprazole.
- MOA: PPIs inhibit the acid-secreting $H^+K^+ATPase$ pumps permanently inactivating them.
- Half-life of PPIs = 18 hours.
- Omeprazole has only oral formulation; all others have IV forms.
- Lansoprazole and esomeprazole have high oral bioavailability.
- All PPIs are prodrugs and their active form is the 'sulfenamide' cation formed within gastric parietal cells.
- Dosage is once daily - most effective when given half hour before breakfast.
- PPIs are the most potent acid inhibitory agents available. They inhibit 90% of 24-hour acid secretion compared to 65% for H_2 -receptor antagonists.
- PPIs are DOC for peptic ulcer disease, gastroesophageal reflux disease and *H. pylori* eradication (as part of the regimen).
- Hepatic cytochrome P450 can be inhibited by the earlier PPIs (omeprazole, lansoprazole).
- Long-term PPI usage has been a/w higher incidence of community-acquired pneumonia and hospital acquired *Clostridium difficile*-associated disease.

 H_2 Receptor antagonists

- Drugs: Cimetidine, ranitidine, famotidine, nizatidine
- MOA: Inhibit histamine H_2 receptor on parietal cells and suppress acid secretion

ANTIEMETICS

Treatment	Mechanism	Examples	Clinical Indications
Antiemetic agents	H_1 Antihistamines	Dimenhydrinate, meclizine, cyclizine, cinnarizine, promethazine	Motion sickness, inner ear disease
	Anticholinergic	Scopolamine, dicyclomine	Motion sickness, inner ear disease
	Antidopaminergic	Prochlorperazine, Thiethylperazine	Medication-, toxin-, or metabolic-induced emesis
	5-HT ₃ antagonist	Ondansetron, granisetron	Chemotherapy- and radiation-induced emesis, postoperative emesis

- Presently this class of drugs is mainly used as a part of anti-*H. pylori* regimen.
- Cimetidine has endocrinal side effects (since it inhibits binding of dihydrotestosterone to androgen receptors - can cause impotence, gynaecomastia in males and galactorrhea in females) on long term use. It also has potent cytochrome P450 inhibitor.

Anticholinergic

- Drugs: Pirenzepine, telenzepine
- MOA: selective M1 receptor blocker; reduction of gastric acid secretion; not used routinely.

Neutralization of gastric acid

- Systemic antacids: sodium bicarbonate, sodium citrate
- Non-systemic: Aluminium hydroxide, Magnesium trisilicate, Magaldrate, Magnesium hydroxide, calcium carbonate.
- Miscellaneous adjuvants to antacids: Alginates, simethicone

Ulcer Protectives

- Sucralfate
- Colloidal bismuth subcitrate
- PG analogue: Misoprostol (PGE1 derivative);

Anti-*H. pylori* drugs

- The regimens have been mentioned in Surgery chapter (Pg 880).

EXTRA EDGE

- Carbenoxolone is an ulcer healing drug that is obsolete now due to its adverse effects (mineralocorticoid effects like HTN, hypokalemia) and availability of better drugs.

Contd.

Treatment	Mechanism	Examples	Clinical Indications
Prokinetic agents	NK1 (neurokinin) antagonist	Aprepitant, fosaprepitant	Chemotherapy-induced nausea and vomiting
	Tricyclic antidepressant	Amitriptyline, nortriptyline	Chronic idiopathic nausea, functional vomiting, cyclic vomiting syndrome
	5-HT ₄ agonist and antidopaminergic	Metoclopramide	Gastroparesis
	Motilin agonist	Erythromycin	Gastroparesis, ?intestinal pseudo-obstruction
	Peripheral antidopaminergic	Domperidone	Gastroparesis
	5-HT ₄ agonist	Tegaserod	Constipation predominant irritable bowel syndrome, ?Gastroparesis, ?intestinal pseudo-obstruction, Gastroesophageal reflux disease
Special settings	5-HT ₃ antagonist with weak 5-HT ₄ antagonism	Cisapride	Intestinal pseudo-obstruction
	Somatostatin analogue	Octreotide	Anticipatory nausea and vomiting with chemotherapy
	Benzodiazepines	Lorazepam	Chemotherapy-induced emesis
	Glucocorticoids	Methylprednisolone, dexamethasone	?Chemotherapy-induced emesis

EXTRA EDGE

- Newer congeners of cisapride like mosapride, renzapride and zacopride do not cause QT prolongation or arrhythmias like cisapride.
- Tegaserod is a gastric prokinetic agent, a CCK receptor agonist developed for treating constipation.

DRUGS FOR CONSTIPATION

Medications for the Management of Constipation

Class	Examples	Comments
Stimulant laxatives	Prune Juice Senna Bisacodyl	These agents directly stimulate peristalsis and may reduce colonic absorption of water
Osmotic laxatives	Lactulose Magnesium hydroxide (Milk of Magnesia) Magnesium citrate	These agents are not absorbed. They attract and retain water in the gastrointestinal tract.
Stool softeners	Sodium docusate Calcium docusate	These agents work by increasing water secretion and as detergents, increasing water penetration into the stool
Suppositories and enemas	Bisacodyl Sodium phosphate enema	

EXTRA EDGE

- Drug useful in opioid induced constipation is alvimopan which acts by binding to μ opioid receptors in GIT and hastens GI recovery without antagonizing central effects of opioids.
- Laxative abuse (anthranoid laxatives, senna) causes ammonium urate kidney stones.

DRUGS FOR DIARRHEA

Opioid Antagonists

- Drugs: Loperamide, diphenoxylate, difenoxin, racecadotril.
- MOA: Act by stimulation μ receptors (decreases intestinal motility) and δ receptors (decreases secretions) present on small and large intestine.

Anticholinergics

- Drugs: Dicyclomine, hyoscyamine.
- Decrease intestinal motility and cramps. Used in combination with opiates.

Alpha Adrenergic Agonists

- Clonidine facilitates absorption, increases intestinal transit time and inhibits secretion of fluids/electrolytes.
- Used in diabetic diarrhea and diarrhea caused by opiate withdrawal.

Octreotide

- **Synthetic somatostatin receptor agonist** that decreases GIT motility, intestinal secretions and inhibits 5-HT, gastrin, CCK, motilin and pancreatic polypeptide.
- Hence, mainly used to treat **secretory diarrheas due to carcinoid tumors** and VIPomas.

APPETITE SUPPRESSING/ANTI OBESITY DRUGS

Drug	Comments
Naradrenergic agents:	Increase extraneuronal noradrenaline by enhancing its release
Amphetamine	High abuse potential
Mozindal	Nonamphetamine, indole derivative, long acting, has additional peripheral effect of increasing the metabolic rate
Phentermine	Available as resin also
Diethylpropion	Short half-life of 4-6 hours
Phenylpropionamine	Blocks NA uptake by inhibiting α_1 adrenergic receptors

Contd...

CENTRAL NERVOUS SYSTEM

OPIOID ANALGESICS AND ANTAGONISTS

Characteristics of Opioid Receptors

	Mu	Kappa	Delta	NOP (Nociceptin)
Distribution	Periaqueductal grey; nucleus solitarius; area postrema; dorsal horn	Cerebral cortex; striatum; midbrain, hippocampus; dorsal horn; medulla	Same as for kappa + trigeminal nucleus; myenteric plexus	Hippocampus; cerebral cortex; sensory neurons; descending pain control circuit
Agonist	Methadone Endorphin Endomorphine 1 and 2	Dynorphin A	Enkephalins	Nociceptin
Antagonist	Beta-funaltrexamine Naloxanazine	Norbinal-torphanimine	Naltrexone	Naloxone

EXTRA EDGE

- **Analgesia, euphoria, constipation** are more at **mu-2 receptors**; **physical dependence** is more at **mu-1** receptor.
- **Dysphoria** is more with **kappa receptor**.
- **Naloxone and Naltrexone** are opioid antagonists at **all 3 types** of opioid receptors (**mu > kappa > delta**).

Contd...

Drug	Comments
Serotonergic agents:	Release serotonin and block its reuptake
Fenfluramine, Dexfenfluramine	SE: Valvular heart defects, pulmonary hypertension, sudden deaths, echocardiographic abnormalities
Newer drugs	
Sibutramine	Blocks uptake of both serotonin and NA in the CNS. SE: Dry mouth, anorexia, constipation, insomnia and dizziness. In some (<5%) patients it markedly increases BP.
Oriostat	Inhibitor of gastric and pancreatic lipase.
Lorcaserin	Selective serotonin receptor agonist SE: psychiatric disturbance; valvular heart disease; breast tumors in animal studies
Liraglutide	Injectable Incretin (Glucagon like peptide-1 receptor agonist) SE: Constipation, hypoglycemia
Phentermine + Topiramate	Tachycardia, mood changes
Naltrexone + Bupropion	Tachycardia, Suicidal thoughts

Contd...

Opioid Analgesics

Morphine Analogs

- Agonists: Morphine, diamorphine (heroin), codeine, pholcodine, levorphanol.
- Partial agonists: Nalorphine, levallorphan
- Antagonists: **Naloxone, Naltrexone, Nalmefene**

Synthetic Derivatives Unrelated to Morphine

- Agonists: Pethidine (meperidine); fentanyl, sufentanyl, remifentanyl, methadone, oxycodone, etorphine, dextropropoxyphene.
- Partial agonists: Pentazocine, Nalbuphine, Butorphanol, Buprenorphine.

Mu Receptor Agonist with Other Mode of Action

- Tramadol, Tapentadol

Those Lacking Analgesic Activity but have Other Uses

- Loperamide; Noscipine; Diphenoxylate; Dextromethorphan.

Morphine

- Central Pharmacological Effects
 - Analgesia: through **mu** receptors, morphine increases pain threshold. More effective against deep seated visceral pain (MI, renal colic, cancer pain).
 - **Euphoria**: sense of well being (**mu** receptors); **dysphoria**: restlessness (**kappa** receptors).
 - Sedation
 - Respiratory depression (mu receptors)
 - Cough suppression
 - Miosis
 - Nausea and vomiting
- Peripheral pharmacological effects
 - Peripheral analgesia
 - GIT: **constipation** by increasing sphincter tone and decreasing GI motility ("**Straub tail reaction**": rats and mice after administration of morphine present with raised stiff tail by spasm of the muscle at the base of the tail).
 - Biliary tract: constriction of sphincter of Oddi - **avoid in pancreatitis**
 - Urinary bladder: **Difficulty in urination**

Uses of Opioids

- **Anaesthetic**:
 - MI, renal colic, cancer pain and traumatic pain.
 - **Patient controlled analgesia (PCA)**: IV Fentanyl used through indwelling catheter by patients themselves
- **Acute LVF**: Morphine decreases cardiac preload (reduced venous tone) and after load (reduced peripheral resistance); it reduces anxiety also.
- **Anti-tussive** (cough suppressant): codeine, dextromethorphan, noscapine.
- **Anesthetic practice**: **Fentanyl** is used in **neurolept analgesia** and in anesthesia during **CABG** (no CVS side effects).
- **Diarrhea treatment**: Loperamide; Diphenoxylate.

Tolerance and Dependence to Opioids

- It is a **cellular adaptive type** of tolerance.
- Tolerance develops to analgesia, euphoria, sedation, and respiratory depression BUT NOT to **miosis, constipation and convulsions (MCC)**
- **Physical dependence** > psychological.
- **Acute Opioid intoxication** and opioid withdrawal are discussed in **Psychiatry** chapter (Pg 1110).

Mixed Agonist-Antagonist and Partial Agonists

- All below drugs are used for moderate to severe pain
- **Pentazocine**: Oral tablet; used for post-operative pain; contra-indicated in MI, epileptic cases, psychoses and head injury.
- **Nalbuphine**: 5 times more potent than pentazocine; used IV or IM; used for moderate to severe pain and for obstetric analgesia.
- **Butorphanol**: Given IV; nasal spray also available
- **Buprenorphine**
- **Nalorphine** (obsolete)

DRUGS FOR EPILEPSY (ANTI-EPILEPTICS)

Drugs	Adverse effects
MOA: Inhibition of voltage-dependent sodium channels	
Carbamazepine	Hyponatremia, cholestatic jaundice, hepatotoxicity, SJS (a/w HLA-B 1502), Drowsiness, ataxia, Vertigo, diplopia, Blurred vision, Agranulocytosis, Aplastic anemia, induction of cytochrome P-450, teratogenic, acute oliguria with hypertension; cardiac conduction defects; MAY exacerbate myoclonic seizures
Oxcarbazepine	Same as above
Phenytoin (diphenyl-hydantoin)	Gingival hyperplasia, hirsutism, lymphadenopathy, SJS, osteomalacia, nystagmus, ataxia, megaloblastic anemia Induction of cytochrome P-450, teratogenic
Lamotrigine	SJS, visual disturbance, dyspepsia, ataxia

Contd...

Contd...

Drugs	Adverse effects
Zonisamide	Renal stones; hypohidrosis, anorexia. DO NOT use in sulfonamide allergy
Lacosamide	GI irritation, PR interval prolongation, cardiac dysrhythmia
MOA: Inhibition of neuronal calcium channels	
Ethosuximide	SJS, Bone marrow suppression
MOA: Enhanced GABA activity	
(GABA receptor agonists - Phenobarbitone and BZDs)	
(GABA reuptake inhibitor - Tiagabine)	
(GABA transaminase inhibitors - Vigabatrin)	
Phenobarbital, pentobarbital	Sedation, tolerance, dependence, rebound seizures, learning difficulty; hyperactivity if used during pregnancy, folic acid supplementation is compulsory since phenobarb is a potent hepatic enzyme inducer and enhances the metabolism of folic acid.
Benzodiazepines, BZDs (clobazam, clonazepam)	Sedation, tolerance, dependence, rebound seizures
Tiagabine	Speech/language problems, abdominal pain, diarrhea, renal calculi, psychosis, tremor, DO NOT use in sulfonamide allergy
Vigabatrin	Peripheral visual field loss (tunnel vision); SJS
MOA: Inhibition of sodium channels (at high doses) and enhanced GABA activity	
Sodium Valproate (valproic acid)	Hepatotoxicity (fatal liver failure in children), transient alopecia, teratogenic (spina bifida), thrombocytopenia, hyperammonemia, PCOD, pancreatitis (rare), alopecia, weight gain
MOA: Inhibition of NMDA-glutamate receptors and enhanced GABA activity	
Topiramate	Weight loss, cognitive impairment, heat intolerance, kidney stones, acute angle closure glaucoma, acute myopia, hyperthermia, hypohidrosis
Felbamate	Weight loss, hepatic failure, aplastic anemia (written consent required). Reserved for refractory seizures
Perampanel	Aggressive behavior
MOA: Unknown (potential enhanced GABA mechanism)	
Gabapentin	Weight loss, edema
MOA: Neuronal potassium channel openers	
Ezogabine (Retigabine)	Retina abnormalities; skin discoloration, QT prolongation, urinary retention
MOA: Selective binding to synaptic vesicle protein 2A (SV2A)	
Levetiracetam; Brivaracetam	Anemia, leukopenia
MOA: Multiple MOAs	
Rufinamide	Leukopenia, QT Interval shortening

Key: GABA: gamma Amino Butyric Acid; MOA: Mechanisms of action; NMDA: N-Methyl D Aspartate.

EXTRA EDGE

- Almost all antiepileptics have CNS side effects of sedation, confusion, dizziness and ataxias. Hence only the special side effects are mentioned in above table - all are important!
- ALL anti-epileptics are potentially teratogenic.
- **Rufinamide**: inhibits voltage dependent Na⁺ channels; **inhibits mGluR5** (metabotropic glutamate subtype 5 receptor).
- **Lacosamide** inhibits **CMRP-2** (Collapsin-Response-Mediator-Protein).
- **Trimethadione** is NOT used now - it caused **hemeralopia** ('day blindness' due to excess glare and photophobia) and is **highly teratogenic**.
- **Endogenous Antiseizure Substance** (that prevents seizures) is **Adenosine**.
- **Vagus Nerve Stimulation** (VNS) has been FDA approved as a treatment option for **partial complex seizures**.

Drugs of Choice

- **Sodium valproate**: is the **DOC for generalised tonic clonic seizures, myoclonic seizures and absence seizures** (H'son - 19th/2552).
- **Vigabatrin** is the **DOC for infantile spasms a/w tuberous sclerosis**.

More About Phenytoin

- Phenytoin is **80-90% protein bound**.
- The kinetics of metabolism of phenytoin is capacity limited; changes from first order to **zero order** over the therapeutic range.
- When given by IM injection, phenytoin precipitates out at the injection site and is absorbed slowly and erratically. **IM route is NOT**, therefore, recommended.
- Large amounts of **folic acid** may counteract the anti-epileptic action of phenytoin, phenobarbitone.

DRUGS FOR PARKINSON'S DISEASE (PD)

Treatment — Anti-Parkinson's Drugs

- **Levodopa (dopamine precursor/prodrug)**
 - Early adverse effects: nausea and vomiting, *postural hypotension, cardiac arrhythmias, exacerbation of angina, alteration in taste sensation*
 - Late adverse effects: abnormal movements, nightmares, **end of dose deterioration, on-off effect**
 - **Pyridoxine** enhances peripheral decarboxylation of levodopa - less is available to cross to the brain - thus **abolishes therapeutic effect of levodopa**
- **Carbidopa and benserazide** (peripheral dopamine decarboxylase inhibitor)
 - They reduce levodopa metabolism - increase its availability and make more of it available to cross to the brain - hence **practically always given with levodopa**.
 - **Co-careldopa** - combination of levodopa with carbidopa
- **Bromocriptine** (dopamine D2 receptor agonist)
 - Increases response to levodopa in patients with declining response; **used as supplement**.
- **Rapinirole, Pramipexole** (nonergot dopamine receptor D2/D3 agonist)
 - Used as **monotherapy for early cases** and as supplement to levodopa.

- These are **also DOC for 'restless leg syndrome'**.
- An **irresistible urge to sleep suddenly** (during driving!) may occur with both above drugs.
- **Pergolide, and piribedil** (dopamine agonists)
- **Selegiline, Rasagiline** (MAO B inhibitor)
 - Used in early cases as monotherapy, may delay the need to start levodopa.
- **Amantidine** (increased synthesis, release and reuptake of dopamine - dopamine facilitator)
 - **More effective against rigidity and bradykinesia** - can be used for brief periods during acute exacerbations; causes ankle edema, **livedo reticularis**
- **Anticholinergics-trihexophenidyl, benhexol, bentrupine** (block cholinergic transmission)
 - Only drugs effective in drug (phenothiazine)-induced PD; Used as adjuvant therapy - **tremor is benefited most**.
- **Entacapone, Tolcapone** (COMT inhibitors)
 - Adjuvants in advanced PD
 - Tolcapone (*rhabdomyolysis, hepatitis* - recently withdrawn in Canada)
- **Surgical treatment of PD - pallidotomy, avoided these days**
- **Deep Brain stimulation**: High-frequency stimulation of the **subthalamic nuclei (MC site)** or **globus pallidus internus** may benefit all the major features of PD.

DRUGS FOR ALZHEIMER'S DEMENTIA

- This has been discussed under CNS in "**Medicine**" chapter (Pg 1090).

DRUGS FOR MULTIPLE SCLEROSIS

- This has been discussed under CNS in "**Medicine**" chapter (Pg 783).

GENERAL AND LOCAL ANESTHETIC DRUGS

- These have been discussed under **anesthesia** chapter.

PSYCHOPHARMACOLOGY

- Antipsychotic drugs; Anti Anxiety drugs; Antidepressants and other psychiatry drugs have been discussed under **psychiatry** chapter.

RENAL SYSTEM

DIURETICS

Diuretic Drug	Site of Action	Mechanism of Action	Indications	Adverse effects
Carbonic anhydrase inhibitors (Acetazolamide, sulfa drug)	PCT	Inhibition of carbonic anhydrase causes mild diuresis and prevents HCO_3^- reabsorption	Glaucoma Epilepsy High altitude sickness , Metabolic alkalosis	Mild metabolic acidosis Hypokalemia , Renal stones , sulfa allergy , paresthesia (tingling extremities) ("Acetazolamide causes ACIDOSIS")
Osmotic agents (mannitol, urea)	PCT, loop of Henle, Collecting tubules	\uparrow tubular fluid osmolarity produces \uparrow urine flow (osmotic gradient \uparrow H_2O excretion)	\uparrow ICP (cerebral edema in head trauma), \uparrow IOP (acute glaucoma), Shock, Drug toxicity	Pulmonary edema , Dehydration CI in renal failure and CHF (can cause fluid overload)
Loop diuretics (Furosemide (sulfa drug), Torsemide, Bumetanide; Ethacrynic acid, non sulfa)	Ascending loop of Henle	Inhibit Na/K/Cl co-transporter to decrease reabsorption and indirectly inhibit Ca reabsorption	CHF Pulmonary edema , Hypercalcemia Rapid onset useful in emergency situations	Otototoxicity (Max with ethacrynic acid) Hyperuricemia (Gout) Hypokalemia , Hypocalcemia ("O God! Loop loses <u>kal</u> or <u>col</u> ")
Thiazides (Hydrochlor-thiazide, chlorthalidone, metolazone)	DCT	Inhibit Na/Cl co-transporter to \downarrow NaCl reabsorption and indirectly \downarrow K^+ excretion and increase Ca reabsorption	HTN CHF Hypercalciuria Diabetes insipidus	Hypokalemic metabolic alkalosis Hyperglycemia , Hyperlipidemia , Hyperuricemia , Hypercalcemia ("HyperGLUC") Impotence
K^+-sparing (spironolactone, eplerenone, amiloride, triamterene)	Collecting tubules	Spironolactone: Aldosterone receptor antagonist that inhibits Na-K exchange; triamterene and amiloride act by blocking Na^+ channels	Secondary hyperaldosteronism CHF	Gynecomastia (spironolactone) Hyperkalemia Menstrual irregularity

Key: Ca, calcium; CHF, congestive heart failure; HCO_3^- , bicarbonate; H_2O , water; HTN, hypertension; K, potassium; Na, sodium; ICP, Intracranial pressure; IOP, Intraocular pressure; PCT, proximal convoluted tubule; DCT, Distal convoluted tubule.

EXTRA EDGE

- **Loop diuretics** are the MC diuretics used in **heart failure**, whereas **Thiazides** are MC diuretic used in treating **HTN**.
- **Bumetanide** (Most potent loop diuretic) is **40 times** more potent than furosemide.
- **Most potent thiazide** diuretic is **polythiazide**.
- **Metolazone** is effective in refractory edema in **chronic kidney disease**.
- **Acetazolamide** is a **weak diuretic** with mainly non-diuretic uses.
- **Indacrinone** (uricosuric diuretic) is an ethacrynic acid analog that is useful for patients of gout requiring diuretic therapy (where loop and thiazide diuretics are contraindicated)

DRUGS RELATED TO BLOOD (ANTICOAGULANT DRUGS)

Natural Anti-coagulant Mechanisms

- The clot does not extend beyond a wound site into the general circulation partly because the fibrin absorbs the thrombin into the clot and inactivates it. Other mechanisms that control blood clotting are:
 - **Prostacyclin (PGI₂)**: Inhibits platelet aggregation.

- **Antithrombin-III (AT-III)**: plasma protein that blocks the action of Factors 9, 10, 11, 12 and 2 (thrombin).
- **Protein C** inactivates factor V and VII.
- **Heparan sulphate**: synthesized by endothelial cells and enhances the activity of AT-III.

ANTICOAGULANTS

Drug	MOA	Adverse Effects
Heparin (More in below table) Parenteral	Activates antithrombin III which \downarrow the activity of thrombin and Xa and prevents clot formation. Monitor PTT	Thrombocytopenia , hemorrhage , osteoporosis; hypersensitivity, narrow therapeutic window , short half life ; for heparin reversal use protamine sulfate
Low molecular weight Heparin (LMWH) Enoxaparin, Dalteparin and other "parins" Parenteral	Binds to factor Xa to prevent clot formation. (Lab monitoring NOT required)	Hemorrhage, fever, and rare thrombocytopenia; NOT easily reversible
Direct thrombin inhibitors Parenteral: Lepirudin, Argatroban, Desirudin, Bivalirudin Oral: Dabigatran	Highly selective inhibitors of thrombin to suppress activity of factors V, IX, and XIII and suppress platelet aggregation	Hemorrhage and hypotension
Direct Factor Xa inhibitors Rivaroxaban, Apixaban, Betrixaban, Edoxaban Oral	Directly engage the active centre of the Factor Xa molecule and inhibit both free Factor Xa in plasma and Factor Xa attached to the pro-thrombinase complex	Hemorrhage
Indirect Factor Xa inhibitors Fondaparinux sodium, Edoxaban sodium Parenteral	Highly selective inhibition of factor Xa without activity against thrombin, require antithrombin as a cofactor and DO NOT inhibit Factor Xa bound to the prothrombinase complex	Hemorrhage, fever, anemia, edema, rash, constipation
Warfarin (Coumadin) Oral	Impairs synthesis and carboxylation of vitamin K-dependent factors II, VII, IX, and X and protein C and protein S. Affects Extrinsic pathway and PT. Follow PT/INR values.	Hemorrhage, numerous drug interactions, and teratogenicity (Canrodi's syndrome); Warfarin is risk factor for calciphylaxis

Unique Points about LMWH Over Heparin

- Low molecular weight heparin (LMWH) can be given **SC (subcutaneous)** due to better bioavailability by this route. Variability in response is minimised.
- These do **NOT** prolong aPTT and clotting times; hence **lab monitoring is NOT required** as with routine unfractionated heparin.
- LMWH has **2-4 times longer half-life**; hence less frequent **once daily dosing** is required.

- **Dose is given in mg** (NOT units) and can be easily calculated on body weight basis.

EXTRA EDGE

- **Idarucizumab**: FDA approved **antidote for Dabigatran** (direct thrombin inhibitor, DTI) associated bleeding.
- **Andexanet alfa**: Investigational agent as antidote for Direct Factor Xa (DFXa) inhibitors ("xaban" drugs).
- **Ciraparontag**: Investigational agent as antidote for DTI and DFXa.

ANTI-PLATELET ANTICOAGULANT DRUGS

Drug	MOA	Adverse Effects
Platelet TXA2 synthesis inhibitor Aspirin (Acetyl Salicylic Acid, ASA)	Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to thromboxane A2 (TXA2) → Inhibits platelet aggregation.	Hemorrhagic stroke GI ulceration and bleeding Tinnitus Reye's syndrome
Platelet P2Y12 inhibitors Thienopyridines (Clopidogrel, Ticlopidine, Prasugrel); Ticagrelor, Cangrelor	Block ADP receptors (P2Y12 receptors) to suppress fibrinogen binding and platelet adhesion to injury sites <i>Ticagrelor and Cangrelor</i> is different from the other three drugs in this group since they are NOT pro-drugs and do NOT require metabolic activation	Thrombocytopenia, Neutropenia (ticlopidine)
Platelet GP IIb/IIIa inhibitors Abciximab, eptifibatide, tirofiban	Inhibit platelet aggregation by binding to platelet GP IIb/IIIa receptors	Nausea, back pain, hypotension
Adenosine reuptake inhibitors Dipyridamole	Inhibit activity of adenosine deaminase and phosphodiesterase to inhibit platelet aggregation	Dizziness, headache, and nausea
Platelet PAR-1 antagonist Vorapaxar	Reversible antagonist of Protease Activated Receptor-1 (PAR-1) (Thrombin binding to PAR-1 results in increased platelet aggregation)	Hemorrhage

Key: ASA, aspirin; CAD, coronary artery disease; DVT, deep vein thrombosis; GI, gastrointestinal; HIT, heparin-induced thrombocytopenia; MI, myocardial infarction; PE, pulmonary embolism; PVD, peripheral vascular disease; PT, Prothrombin Time; PTCA, Percutaneous Transluminal Coronary Angioplasty; SC, SubCutaneous; INR, International Normalized Ratio.

Heparin Vs Warfarin

	Heparin	Warfarin
Structure	Large anionic polymer, acidic	Small lipid soluble molecule
Route given	Parenteral (IV, SC)	Oral
Site of action	Blood	Liver
Mechanism of action	Activates antithrombin III which ↓ the action of thrombin (IIa) and Xa	Impairs synthesis and carboxylation of vitamin K-dependent clotting factors II, VII, IX, and X and protein C and protein S (vitamin K antagonist)
Onset of action	Rapid (within seconds)	Slow, limited by half-lives of clotting factors
Duration of action	Acute (hours)	No
Inhibits coagulation in vitro	Yes	No
Treatment of acute overdose	Protamine sulphate	IV vitamin K and fresh frozen plasma
Monitoring	aPTT /clotting time (intrinsic pathway)	PT/INR (Extrinsic pathway) ("WEPT!!" Warfarin - Extrinsic, monitor PT)
Chemistry	Mucopolysaccharide	Coumarin derivative
Source	Hog lung, pig intestine	Synthetic

EXTRA EDGE

Factors Decreasing Effects of Warfarin: Barbiturates; Rifampicin; Carbamazepine; Griseofulvin; OCPs; Cholestyramine; Diuretics; Vitamin K; Hypothyroidism

Uses of Anticoagulant and Antiplatelet Drugs

- Prevention and treatment of DVT and pulmonary embolism.
- Myocardial infarction: to reduce thromboembolic complications.
- Rheumatic heart disease: in atrial fibrillation patients with high risk of stroke.

Thrombolytics

- Streptokinase, Urokinase, tPA** (tissue plasminogen activator, **alteplase**), **ASPAC (anistreplase)**
- Mechanism of Action:** Directly or indirectly aid **conversion of plasminogen to plasmin**, the major fibrinolytic enzyme which cleaves thrombin and fibrin clots.

lytic enzyme which cleaves thrombin and fibrin clots. ↑APTT, ↑PT, low in platelet count.

- Clinical **indications:** **Early MI, Early ischemic stroke**
- Adverse effects: Bleeding; CI in active bleeding, h/o intracranial bleeds, recent surgery, or severe HTN. Treat with **aminocaproic acid**, an inhibitor of fibrinolysis.

Antifibrinolytics

- These drugs **decrease fibrinolytic activity** and are useful in hemophiliac patients undergoing surgery.
- Aminocaproic acid.**
- Tranexemic Acid.**

ANTIBACTERIAL THERAPY

Bacteriostatic drugs	Bactericidal drugs	Mechanism of action	Drugs
Sulfonamides, Spectinomycin, Chloramphenicol, Clindamycin, Erythromycin, Ethambutol, Novobiocin, Tetracycline, Linezolid ("V ² C ² NT ² L ¹ ").	Vancomycin, Aminoglycosides, Fluoroquinolones, Polypeptides, Penicillin, Pyrazinamide, Isoniazid, Cephalosporins, Metronidazole, Rifampicin, ("V Are Fully Professional Cell Murderers!")	Inhibitors DNA gyrase	Fluoroquinolones
		Interfere with DNA function	Rifampicin
		Block mycolic acid synthesis	Isoniazid
		Interfere with intermediary metabolism	Sulfonamides, sulfones, PAS, pyrimethamine, metronidazole

Mechanism of Action of Antibacterial Drugs

Mechanism of action	Drugs
Inhibit cell wall synthesis	Penicillins, cephalosporins, cycloserine, vancomycin, bacitracin
Cause leakage from cell membranes	Polypeptides: Polymyxin, Colistin, bacitracin; Polyenes: Amphotericin B, Nystatin, Hamycin
Block protein synthesis	Chloramphenicol, tetracyclines, macrolides, clindamycin, streptogramins (quinupristin, dalbapristin), linezolid
Cause misreading of mRNA code and affect permeability	<u>Aminoglycosides</u>
Interfere with DNA synthesis	Acyclovir, zidovudine
Block nucleotide synthesis by inhibiting folate metabolism	Sulfonamides, trimethoprim

Antimicrobials Needing Dose Reduction in Renal Failure

Reduce dose even in mild failure	Reduce dose only in severe failure
<ul style="list-style-type: none">AminoglycosidesAmphotericin BAcyclovirEthambutolVancomycinTetracyclines (better avoid)	<ul style="list-style-type: none">CarbenicillinCotrimoxazoleCefotaximeFluoroquinolonesMetronidazole

Antibiotics obtained from

Fungi	Penicillin, Griseofulvin, Cephalosporin
Bacteria	Polymyxin B, Colistin, Tyrothricin, aztreonam, bacitracin
Actinomycetes	Aminoglycosides, tetracyclines, chloramphenicol, macrolides, polyenes

Resistance Mechanisms for Various Antibiotics

Drug	Most common mechanism
Penicillins/ Cephalosporins	Beta-lactamase cleavage of B-lactam ring, or altered PBP in case of MRSA (<i>mecA</i>) gene
Aminoglycosides	Modification via acetylation, adenylation, or phosphorylation
Vancomycin	Terminal D-al a of cell wall component replaced with D-lac ; L affinity
Chloramphenicol	Modification via acetylation
Macrolides, Tetracycline	Methylation of rRNA near erythromycin's ribosome-binding site uptake or I transport out of cell
Sulfonamides	Altered enzyme (bacterial dihydropteroate synthetase), L uptake, or 1 PABA synthesis
Quinolones	Altered gyrase or reduced uptake

Penicillin G and Penicillin V (Beta lactamase sensitive penicillins)

- **Penicillin-V**: Acid stable and can be given **orally**.
- **Penicillin G**: Acid labile and given **IM or IV only**. **Procalne penicillin G** and **Benzathine penicillin G** are **depot IM formulations** of penicillin G.
- **Penicillin G** is **excreted by kidneys** - dose adjustment in renal failure required.
- **Penicillin G** is the **DOC** for these infections caused by Gram-positive bacilli: **Clostridium tetani** (tetanus); **Clostridium perfringens** (gas gangrene); **Corynebacterium diphtheriae** (diphtheria); **Bacillus anthracis** (anthrax) and **Listeria monocytogenes** (meningitis, listeriosis).
- **Penicillin G (Benzathine)** is the **DOC** for **T.pallidum (syphilis)** - all types - congenital; neurosyphilis and syphilis during pregnancy.

Beta-lactamase (penicillinase) Resistant Penicillins

- **Cloxacillin, Dicloxacillin, flucloxacillin** (Oral, IM)
- **Methicillin, Nafcillin** (IM only)
- Above drugs are additionally effective against *Staphylococcus aureus* - hence **anti-staphylococcal penicillins**.
- **Methicillin** no longer used - **interstitial nephritis**; but staphylococci resistant to cloxacillin and nafcillin are also historically called Methicillin resistant *Staphylococcus aureus* (MRSA)

Aminopenicillins (Ampicillin, Amoxicillin)

- **AmOxicillin** has greater **Oral** bioavailability than ampicillin.
- Extended-spectrum penicillins - certain gram-positive bacteria and Gram-negative bacilli (*Hemophilus influenzae*, *E. coli*, *Proteus mirabilis*, *Salmonella*, enterococci), but NOT against *Pseudomonas*
- SE: Hypersensitivity; ampicillin - rash; pseudomembranous colitis.

Anti-pseudomonal penicillins

- **Ticarcillin, Carbenicillin, Piperacillin, Mezlocillin, Azlocillin** - ALL parenteral
- ("Thick Carbon Pipe")

BETA LACTAM ANTIBIOTICS

- Beta lactam antibiotics are so called since all of them have a **beta lactam ring** as a common feature in their chemical structure.
- They include **penicillin, cephalosporins, carbapenems** and **monobactams**.
- MOA: **Inhibition of bacterial cell wall synthesis**.
- **Beta-lactamase (penicillinase)** are enzymes produced by bacteria that provide resistance to penicillin.

PENICILLIN

- **Alexander Fleming** discovered penicillin.
- Penicillin was originally obtained from the fungus **Penicillium notatum**, but at present the high yielding source is **Penicillium chrysogenum**.
- **Natural** penicillins are **Penicillin V** and **Penicillin G**.
- MOA: Bind penicillin-binding proteins (PBP) in cell wall of all bacteria - **Block transpeptidation and cross-linking** of bacterial cell wall - thus **inhibit bacterial cell wall synthesis** - **bactericidal**.

Beta lactamase inhibitors

- Addition of beta lactamase inhibitors enhances the spectrum of action of some penicillins
 - **Clavulanic acid** (oral) used with amoxicillin
 - **Sulbactam** (IV/IM) used with ampicillin
 - **Tazobactam** (IV/IM) used with piperacillin

Other Beta Lactam Antibiotics

Monobactams (Aztreonam)

- Antibacterial spectrum resembles that of aminoglycosides; synergistic with aminoglycosides.
- Clinical use: **Aerobic Gram-negative** infections - *Klebsiella*, *Pseudomonas*, *Serratia*, *Proteus*, *Citrobacter*, *Enterobacteriaceae*.
- **NO** activity against Gram-positives or anaerobes.
- **SE** Usually nontoxic; occasional GI upset. No cross-sensitivity with penicillins or cephalosporins.
- **CAN** be **safely used** in **penicillin and cephalosporin -allergic patients** (except **ceftazidime allergy**); can also be used in those with renal insufficiency who cannot use aminoglycosides.

Contd...

Contd...

Carbapenems

- Examples: Imipenem, meropenem, Ertapenem, Doripenem, Faropenem, Razupenem.
- Carbapenems are **beta-lactamase resistant**.
- Clinical use: **DOC for Enterobacteria**.
- **Imipenem** is always administered with **cilastatin** (inhibitor of renal dihydropeptidase I) to decrease inactivation in renal tubules.
- SE: GI distress, skin rash, and **seizures** at high plasma levels
- Other "**penems**" however, have a reduced risk of seizures and is stable to dihydropeptidase I.

EXTRA EDGE

- **All types** of allergic reactions (type 1 to type 5) can occur with penicillin.
- Other reactions thought to have an allergic basis include nephritis (a/w methicillin); hepatitis (a/w oxacillin); leukopenia and severe skin rashes.
- The frequency of cross-allergy between cephalosporins and penicillins is not known but is estimated to be about **6-10%**. Persons with a history of anaphylaxis to penicillins should **NOT** receive cephalosporins.

Other Bacteria that Inhibit Cell Wall Synthesis

Vancomycin

- MOA **Inhibits cell wall mucopeptide formation** by binding D-al
- D-al portion of cell wall precursors. Bactericidal. Resistance occurs with amino acid change of D-al
- D-al to D-al
- Used for serious, **aerobic gram-positive multidrug-resistant organisms**, including
- It is the **DOC** for **MRSA**.
- **Second DOC** for **Clostridium difficile** (pseudo-membranous colitis, PMC).
- **SE** Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing - "**red man syndrome**" (can largely prevent by pretreatment with antihistamines and slow infusion rate).

Telcoplanin

- MOA **Similar to vancomycin**.
- More active against enterococci than vancomycin.
- Used for endocarditis prophylaxis, for PMC.
- **SE** **bronchospasm** rarely

Talavancin, Dalbavancin, Ortipavancin

- **Similar to Vancomycin** in MOA and uses
- **SE** Can interfere with coagulation tests

Daptomycin

- **Similar to vancomycin** BUT cannot be used for treating pneumonia as it is **inactivated by pulmonary surfactant**
- **SE** Myopathy, eosinophilic pneumonia

Bacitracin

- Mainly a **topical antibiotic** - active against staphylococcus aureus, streptococcus pyogenes and clostridium difficile.

Fosfomycin

- Active against gram positive and gram negative bacteria
- Synergistic action with other antibiotics.
- A single 3 gram dose is used to treat uncomplicated lower **UTI** in women.
- **Safe in pregnancy**

Cycloserine

- **SE** **Extensively** used as **second line drug** for TB.

EXTRA EDGE

- **Bacterio that inhibit cell wall synthesis** are:
 - **Beta lactams:** Penicillin, cephalosporins, monobactams, carbapenems
 - **Glycopeptides:** Vancomycin, Teicoplanin
 - **Others:** Bacitracin, Fosfomycin, Cycloserine, Daptomycin

CEPHALOSPORINS

- **Cephalosporins are similar to penicillins** chemically and in mechanism of action.
- Except for the first generation, the rest are more resistant to beta lactamase and have a **broader spectrum** of activity.
- However, **except Fifth generation, NO** cephalosporin of I-IV generation is active against MRSA.

Generations of Cephalosporins

First Generation	
Oral	Parenteral
Cephalexin Cefadroxil	Cefazolin
Second Generation	
Oral	Parenteral
Cefprozil Cefuroxime axetil Cefaclor	Cefuroxime Cefoxitin
Third Generation	
Oral	Parenteral
Cefexime Cefpodoxime proxetil Ceftibuten Cefdinir Ceftamet pivoxil	Cefotaxime Ceftizoxime Ceftriaxone Ceftazidime Cefoperazone
Fourth Generation	
Oral	Parenteral
	Cefepime Cefpirome Cefozopran
Fifth Generation	
Oral	Parenteral
	Ceftaroline

EXTRA EDGE

- Cephalosporins that have a **methylothiotetrazole group** (e.g. cefamandole, cefmetazole, cefoperazone, cefotetan) cause **hypoprothrombinemia** and severe **disulfiram-like** reaction with alcohol.
- Drugs excreted to large extent **through bile** such as **ampicillin, ceftriaxone** and **cefoperazone** are prone to cause **diarrhoea**.
- **Ceftriaxone** has been a/w **cholelithiasis**.

AMINOGLYCOSIDES

- MOA: **Bactericidal**; inhibit formation of initiation complex and cause **misreading of mRNA code**; bind to 16S ribosomal RNA of the 30S subunit.
- Clinical use: Severe **Gram-negative rod infections**. Synergistic with beta-lactam antibiotics. **Neomycin** useful for **bowel surgery**.
- Require oxygen for uptake; therefore **ineffective against anaerobes**.
- Side Effects:
 - **Nephrotoxicity** (especially when used with cephalosporins)
 - **Ototoxicity** (especially when used with loop diuretics)
 - **Neuromuscular blockade**: When given along with neuromuscular blocking agents, aminoglycosides can aggravate the neuromuscular blockade.

Toxicity of Aminoglycosides

- Most vestibulotoxic: Streptomycin
- Most cochleotoxic: Amikacin
- Most nephrotoxic: Neomycin
- Least nephrotoxic: Streptomycin
- Maximum neuromuscular blockade: Streptomycin

About Individual Aminoglycosides

- **Gentamicin**: MC used aminoglycoside.
- **Streptomycin**: It is used rarely in combinations only since resistance emerges fast; Now it is a reserve (supplemental) first line drug for TB.
- **Sisomicin**: similar to gentamicin.
- **Tobramycin**: currently used against Pseudomonas.
- **Kanamycin**: NO longer used due to high toxicity.
- **Arbekacin**: useful against MRSA.
- **Spectinomycin**: Not a true aminoglycoside; can be used as alternative treatment for **gonorrhea in penicillin allergic patients**.
- **Paromomycin**: useful for intestinal amebiasis and against cryptosporidium parvum.

MACROLIDES AND RELATED DRUGS

Macrolides

- Erythromycin (prototype); Roxithromycin, Clarithromycin, Azithromycin, Spiramycin
- MOA: **Inhibit protein synthesis** by blocking translocation; bind to the 23S rRNA of the 50S ribosomal subunit. **Bacteriostatic**.
- Uses:
 - **Macrolides are highly effective** for atypical pneumonia (*Mycoplasma*); *Legionella* pneumonia; *Bordetella* (whooping cough) and eradication of C.diphtheria from pharyngeal carriers.
 - **Spiramycin** is highly effective against *Toxoplasma gondii* and *Cryptosporidium*
 - **Clarithromycin** is also effective against MAC (*M. avium complex*); *H. pylori* and *M. leproe* (with minocycline).
 - **Azithromycin** is highly active against *Chlamydia*
 - Side Effects: **GI discomfort** (MC cause of noncompliance), **acute cholestatic hepatitis** (erythromycin estolate), eosinophilia, skin rashes, **QTc prolongation**
 - Erythromycin, clarithromycin (**NOT azithromycin**) inhibit CYP3A4 isoenzyme which can lead to drug interactions. They increase serum concentration of **theophyllines, oral anticoagulants**.

Lincosamides (Lincomycin, Clindamycin)

- Lincomycin is NO longer in use
- MOA: same as macrolides.
- Uses:
 - Topically in **acne** treatment
 - DOC for *bocteroides fragilis*
 - Clindamycin + pyrimethamine used for *T.gondii*
 - Clindamycin + primaquine used as **alternative** to cotrimoxazole for treating *P.firovecii* pneumonia
 - **St. Diarrhea and pseudomembranous colitis**

Ketolides (Telithromycin)

- A semisynthetic derivative of erythromycin having a **3-keto group** which is crucial in conferring **sensitivity to macrolide resistant strains**.
- MOA: same as macrolides
- Mainly indicated for **macrolide resistant community acquired pneumonia**

Oxazolidinones

- Drugs: **Lizeolid** (prototype); **Tedizolid**, **Radezolid**, **Torezolid**
- MOA: Inhibits bacterial protein synthesis - same as macrolides.
- Effective against **Gram positive** pathogens ONLY.
- Reserved for treatment of **infections caused by multi-drug resistant bacteria** - VRSA, MRSA etc.; Also approved for **diabetic foot**.
- **St. Myelosuppression, optic neuropathy** - with prolonged use. Linezolid inhibits MAO - can cause **'cheese reaction'** with tyramine containing foods

Contd...

Contd...

Streptogramins (Pristinamycin)

- Synergistic combination of streptogramin B (quinupristin) and streptogramin A (dalfopristin) in 30:70 ratio.
- MOA: inhibit bacterial protein synthesis
- Similar spectrum of activity to macrolides and lincosamides for Gram-positive bacteria, with a reduced risk of drug resistance.
- Used **IV only**; can cause infusion related arthralgia-myalgia syndrome

Polymyxin B and Colistin

- MOA: inhibit bacterial protein synthesis
- Used only **topically** now for skin, eye and ear infections in combination with other drugs.
- A/w **nephrotoxicity and neurotoxicity** when used systemically

Mupirocin

- Obtained from *Pseudomonas fluorescens*
- MOA: inhibit bacterial protein synthesis
- Used as **topical ointment** for Staphylococci and Streptococci - impetigo, folliculitis etc..

Pleuromutilins (Retapamulin)

- MOA: inhibit bacterial protein synthesis
- Used as **topical ointment** for Staphylococci and Streptococci - impetigo, folliculitis etc..

Fusidic Acid

- MOA: inhibit bacterial protein synthesis
- Used as **topical ointment** for Staphylococci and Streptococci - impetigo, folliculitis etc..

EXTRA EDGE

- Non-antibiotic uses of erythromycin: It is a **motilin receptor agonist** (used in **diabetic gastroparesis**); **Anti-inflammatory** effect used in arthritis.

BROAD SPECTRUM ANTIBIOTICS

Tetracyclines

- MOA: Inhibits bacterial protein synthesis by binding to 30S ribosomal subunit
- Classification
 - **Short Acting** ($t_{1/2}$ 6-10 hours): Tetracycline, chlortetracycline; oxytetracycline
 - **Intermediate acting** ($t_{1/2}$ 12-13 hours): Demeclocycline, methacycline
 - **Long Acting** ($t_{1/2}$ 18-20 hours): Doxycycline, Minocycline
- Bioavailability of **minocycline** and **doxycycline** is **95-100%**. Food retards absorption of all tetracyclines **except** doxycycline and minocycline.

Uses of Tetracyclines

- ▶ **Tetracyclines are DOC** for treatment of RMSF (Rocky mountain Spotted Fever); Psittacosis; Granuloma Inguinale; Chlamydia pneumonia; Lyme disease (Borrelia burgdorferi) and Relapsing fever (Borrelia recurrentis).
- ▶ **Used along with gentamicin** for treating Brucella, Tularemia and Plague (Y.pestis).
- ▶ **Doxycycline**: can be used in patients with renal disease (lack of nephrotoxicity and biliary excretion).
- ▶ **Demeclocycline** has been used in treating SIADH.
- ▶ **Minocycline** is used for **swimming pool granuloma** caused by *M.marinum*; also **topically** for treating **acne vulgaris** and **periodontitis**.
- Side effects:
 - ▶ **Discoloration of teeth** and **retardation of bone growth** when tetracyclines are given to children < 10 years of age.
 - ▶ Chronic tetracycline use can cause **esophageal and vaginal candidiasis**
 - ▶ **Hepatotoxic** during pregnancy
 - ▶ **Fanconi syndrome** may occur with use of tetracyclines beyond expiry date.
 - ▶ Except doxy and minocycline, **others are nephrotoxic**
 - ▶ **Pulmonary eosinophilia** and **pseudotumor cerebri** can occur.
 - ▶ **Demeclocycline** can induce **nephrogenic diabetes insipidus**
 - ▶ Doxy and demeclocycline can induce **photosensitivity** to sunlight.
 - ▶ **Minocycline** induces **vestibular toxicity**.

Glycyl-Cyclines (Tigecycline)

- ▶ Tigecycline is a **minocycline analog**; MOA is **similar to tetracyclines** BUT 20 times **more potent**.
- ▶ **Effective against MRSA and VRE** (Vancomycin resistant enterococci); Also used for complicated skin/soft tissue infections and intra-abdominal infections.
- ▶ Eliminated through **bile** (NO dose adjustment in renal failure).

Chloramphenicol

- MOA: **Inhibits bacterial protein synthesis by binding to 50S ribosomal subunit** (similar to macrolides). Bacteriostatic (BUT **bactericidal to H.influenzae!**).
- Clinical use: **Meningitis** (Hemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae); Topically used for **conjunctivitis** and ear infections.
- **Conservatively used now** because of toxicities.

- Side Effects:
 - ▶ Dose dependent **bone marrow suppression**;
 - ▶ **Aplastic anemia** (Non-dose dependent in Idiosyncratic reaction);
 - ▶ **"Gray baby syndrome"** (in premature infants because they lack liver UDP-glucuronyl transferase) characterized by progressive cyanosis, abdominal distension hypothermia, CVS collapse and death.
- It is a **potent enzyme inhibitor** and inhibits metabolism of morphine (respiratory depression); Chlorpropamide (hypoglycemia) and warfarin (bleeding).

FLUOROQUINOLONES (FQ)

- Classification: Based on their time of introduction and increasing antibacterial spectrum, FQs are classified as
 - ▶ First Gen: Norfloxacin, Ciprofloxacin, ofloxacin, Pefloxacin, Lomefloxacin
 - ▶ Second Gen: Levofloxacin
 - ▶ Third Gen: Gatifloxacin, Sparfloxacin
 - ▶ Fourth Gen: Moxifloxacin, Finafloxacin
- MOA: Inhibit **bacterial DNA gyrase (topoisomerase II)** **Bactericidal**.
- Clinical use: Gram-negative rods of urinary and GI tracts (Including Pseudomonas), Neisseria, some gram positive organisms.
- Must not be taken with antacids.
- Side Effects: **GI upset, superinfections, skin rashes, headache, dizziness**. Contraindicated in pregnant women and in children because animal studies show **damage to cartilage. Tendinitis and tendon rupture** in adults; **leg cramps and myalgias** in kids, **Hypoglycemia** with gatifloxacin (**banned in India**).

EXTRA EDGE

- Nalidixic Acid is a **non-fluorinated** quinolone used to treat UTI.
- **Nitrofurantoin** blocks bacterial carbohydrate metabolism to inhibiting acetyl CoA synthesis - used as urinary antiseptic in UTI.

SULFONAMIDES

- **Orally Absorbable** agents: Sulfamethoxazole, Sulfadoxine.
- **Orally Non-Absorbable** agents: Sulfasalazine, Olsalazine
- **Topical** sulfonamides: Silver sulfadiazine, Mafenamide, Sulfacetamide.

- MOA: Sulfonamides are PABA analogues that **inhibit bacterial dihydropteroate synthetase (folate synthetase)**. **Bacteriostatic**.
- Sulfamethoxazole + Trimethoprim = **Cotrimoxazole** - used in recurrent UTIs, Shigella, Salmonella, Pneumocystis jiroveci pneumonia.

- **Sulfadoxine + pyrimethamine** combination used **chloroquine resistant P.falciparum malaria**.
- Side Effects: Hypersensitivity reactions, **hemolysis** in G6PD deficiency, **nephrotoxicity** (tubulointerstitial nephritis), photosensitivity, **kernicterus** in infants.

ANTIFUNGAL DRUGS

Echinocandins (Caspofungin, Micafungin, Anidulafungin)

- MOA: **Inhibit synthesis of 1-3 beta glucan** - an essential component of fungal cell wall - thus **inhibit fungal cell wall synthesis**.
- Used **IV** for **invasive candidosis** and **aspergillosis**.
- Adverse effects: Transient **neutropenia**; histamine reactions - flushing; elevated hepatic enzymes.

Polyene group: Amphotericin B

- MOA: **Binds ergosterol** (unique to fungi); forms membrane pores that allow leakage of electrolytes from fungal cell membrane.
- Used **IV only** as **Amphotericin deoxycholate** suspension or as **liposomal Amphotericin B** or **Amphotericin B lipid complex**.
- For IV administration, dilute Amp B powder with **5% glucose/dextrose** solution. Saline makes the suspension very coarse!!
- Used for **wide spectrum of systemic mycoses** (Cryptococcus, Blastomyces, Coccidioides, Aspergillus, Histoplasma, Candida, Mucor). Used intrathecally for fungal meningitis; does **not** cross blood-brain barrier.
- Adverse effects: Serious side effect is **nephrotoxicity** (renal tubular necrosis, hypomagnesemia and hypokalemia due to renal tubular acidosis, azotemia) - **Hydration** reduces nephrotoxicity; arrhythmias, anemia, IV phlebitis Liposomal amphotericin reduces toxicity.
- **Most toxic** antifungal - hence called **amphoterrible!**

Polyene group: Nystatin

- MOA: Similar to amphotericin B
- **Too toxic for systemic** use. Used as mouthwash ("Swish and swallow") for oral candidiasis (**thrush**); topical for **diaper rash** or **vaginal candidiasis**.

Azoles

- Examples: Fluconazole, ketoconazole, clotrimazole, miconazole, itraconazole, voriconazole.
- MOA: **Inhibit fungal steroid (ergosterol) synthesis** and thus results in damaged leaky cell membrane.
- Used for **systemic mycoses** - broad spectrum (Cryptococcus, Blastomyces, Coccidioides, Aspergillus, Histoplasma, Candida, Mucor)
- **Ketoconazole** is replaced by better azoles now; does **NOT** cross blood brain barrier - NOT useful in fungal meningitis. **Inhibits cytochrome P450** - drug interactions and QTc prolongation; inhibits testosterone synthesis and causes **gynecomastia**.

Contd...

Azoles

- **Fluconazole** has **NO activity against Aspergillus**; ALSO least effect on cytochrome P450 of all the azoles.
- **Itraconazole** additionally useful against Tinea (ringworm) infections; can cause **hypokalemia, edema, HTN**.
- **Voriconazole** more effective against **invasive aspergillosis**; hepatic metabolism; transient blurred vision may occur.
- **Posaconazole** is long acting; useful in resistant cases
- **Topical Azoles**: for fungal skin infections Clotrimazole, miconazole.

Flucytosine (5-Fluorocytosine, 5-FC)

- MOA: **Inhibits fungal DNA synthesis** by conversion to fluorouracil, which competes with uracil.
- Used in **systemic fungal infections** (e.g., Candida, Cryptococcus) in combination with amphotericin B.
- Side Effects: **bone marrow suppression**

Griseofulvin

- MOA: Interferes with fungal microtubule function; **disrupts mitosis** - it also binds to newly synthesised keratin making it **resistant to fungal invasion**; It gets deposited in keratin-containing tissues (e.g., nails).
- Used for **oral treatment of superficial fungal infections** (NOT systemic/deep mycoses!); It inhibits growth of dermatophytes (tinea, ringworm).
- Adverse effects: Teratogenic, carcinogenic, confusion, hepatotoxicity, headaches, inducer of cytochrome P450; disulfiram reaction

Terbinafine

- MOA: **Inhibits** the fungal enzyme **squalene epoxidase** which converts squalene to lanosterol; reduced lanosterol = reduced ergosterol = fungal cell membrane damage.
- Used for **oral treatment of superficial fungal infections** - dermatophytoses - especially **onychomycosis** (NOT systemic/deep mycoses!)

Topical Antifungals

- ▶ Azoles: Clotrimazole, Miconazole, Sertaconazole etc.
- ▶ Polyenes: Nystatin.
- ▶ Terbinafine, Butenafine, Naftifene.
- ▶ Ciclopirox, Tolnaftate, Clotrimazole, Benzoic acid, Sodium thiosulphate

Contd...

ANTIVIRAL DRUGS

Drug	Spectrum	Toxicity	Comments
Viral DNA Polymerase Inhibitors			
Acyclovir	HSV, VZV	Neurotoxicity, reversible renal dysfunction	
Valacyclovir	VZV, HSV	HUS-TTP in AIDS patients	Prodrug of acyclovir; more effective in herpes zoster
Ganciclovir	CMV	Neutropneia, thrombocytopenia	Intravitreal implants available for CMV retinitis in AIDS patients
Valganciclovir	CMV	Neutropneia, thrombocytopenia	Prodrug of ganciclovir; used only orally
Penciclovir	HSV	Local reactions	Topical cream only
Famciclovir	HSV, VZV	Angioedema; local reactions	Prodrug of penciclovir; Mainly topical use only; Oral use for Herpes zoster
Idoxuridine	HSV keratitis		Topical drops
Trifluridine	HSV keratitis		Topical drops
Foscarnet	CMV, HSV resistant to acyclovir, VZV, HIV-1	Nephrotoxic, genital ulcers, calcium disturbances	Used IV
Cidofovir	CMV	Neutropenia, nephrotoci, uveitis, ocular hypotony	Used IV
Vidarabine	HSV, VZV	Teratogenic, megaloblastosis, neurotoxic	
Viral Neuraminidase Inhibitors			
Oseltamivir	Influenza A and B	aggravation of diabetes	
Zanamvir	Influenza A and B	Bronchospasm	
Laninamivir	Influenza A and B		Inhalational
Peramavir	Influenza (H1N1)		Given IV
m-RNA synthesis inhibitors			
Ribavirin	RSV, severe influenza A and B, Lassa fever	Wheezing	Used mainly as aerosol
Fomvirsen	CMV	Ocular inflammation, retinal detachment	Used Intravitreal
Inhibitors of viral penetration and uncoating			
Amantadine	Influenza A only	Confusion	
Rimantadine	Influenza A only	Confusion	

Other Important Antivirals

- **Pavilionab:** Humanised monoclonal antibody against **Respiratory syncytial virus**; used in RSV infections.

- **Imiquimod:** Topical antiviral **against HPV** agent used for external genital and perianal **warts**.

Anti- HIV drugs

- These have been covered in detail under AIDS chapter (Pg 301).

ANTI-HELMINTHICS

MCQ points about Mechanism of Action

- Against nematodes
 - ▶ **Pyrantel pamoate and Levamisole:** produce **depolarising neuromuscular blockade** in helminths - they are unable to remain attached to intestinal lumen and are expeled in feces.
 - ▶ **Piperazine** is a **GABA receptor agonist** and activates GABA gated Chloride channels in the worms that causes **flaccid paralysis** of worms.
 - ▶ **Ivermectin** acts on glutamate gated chloride channels in worms.
 - ▶ **DL** Alters microfilarial membrane characteristics so that they are **phagocytosed by tissue fixed monocytes**.
- Against Trematode
 - ▶ **Metrifonate:** **OrganoPhosphorus** compound; MOA similar to Pyrantel pamoate.
 - ▶ **Oxaminquine:** **blocks DNA synthesis** in parasite.
 - ▶ **Bithionol:** **blocks ATP synthesis** in the parasite.
- Against Cestodes
 - ▶ **Niclosamide:** **uncouples oxidative phosphorylation** in cestodes.
 - ▶ Against trematodes as well as cestodes
 - ▶ **Praziquantel:** causes **influx of calcium** from endogenous stores of the cestodes.
- **Broad spectrum anti-helminthics (Albendazole, thiabendazole, mebendazole)**
 - ▶ These **prevent assembly of microtubules** in the worms leading to irreversible inhibition of glucose uptake by the worms.

Anti-Helminthic Drugs of Choice

Parasite	Drug of choice
Trematodes (Flukes)	
Schistosoma	Praziquantel
Clonorchis	
Paragonimus	Praziquantel
Fasciola hepatica	Triclabendazole > Bithionol
Cestodes (Tapeworms)	
Hamia saginata, Taenia solium	Praziquantel
Dlatum	
H. nana	
Cysticercosis	Albendazole
Hydatid disease	

Contd...

Parasite	Drug of choice
Nematodes	
Ascaris (roundworms)	Albendazole
Hookworms (Necator, Ankylostoma)	
Trichuris	
Trichinella	
Enterobius	
Capillaria	
Strongyloides	Ivermectin
Onchocerca	
Wuchereria bancrofti	DEC
Brugia malayi	
Dracunculus (guineaworm)	Metronidazole
Cutaneous Larva migrans	Thiabendazole
Visceral larva migrans	DEC

ANTIMALARIAL DRUGS

Drug	Toxicity	Comments
Chloroquine	Pruritus; postural hypotension; accommodation difficulty; keratopathy,	Good oral absorption, very rapid IM and SC absorption; enormous apparent volume of distribution (Vd > 100L/kg)
Quinine, quinidine	"Cinchonism": tinnitus, high- tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG QTc interval prolongation	Good oral and IM absorption Quinidine is more toxic
Amodiaquine	Nausea	
Primaquine	Nausea, vomiting, diarrhea, abdominal pain, hemolysis, methemoglobinemia	Used for radical cure - eradicates hepatic forms of P.vivax and P.ovale malaria
Mefloquine	Fuzzy thinking, sleeplessness, nightmares, sense of dissociation	
Halofantrine	Diarrhea	
Lumefantrine		

Contd...

Contd...

Contd...

Drug	Toxicity	Comments
Artemisinin and derivatives (artemether, artesunate)	Reduction in reticulocyte count (but not anemia); neutropenia at high doses; in some cases, delayed anemia after treatment of severe malaria with hyperparasitemia	Good oral absorption artesunate and artemether bio-transformed to active metabolite dihydro-artemisinin;
Pyrimethamine		For blood stages only
Proguanil (chloroguanide)		Not used alone for treatment
Atovaquone		Acts mainly on blood stages
Tetracycline, doxycycline	Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, moniliasis (candidiasis), benign intracranial hypertension	Should not be used alone for treatment

Regimens

Condition	Drugs
Chloroquine sensitive strains of <i>P. falciparum</i> , ovale, vivax, malariae	Chloroquine
Uncomplicated <i>P. falciparum</i> resistant malaria	Artemether + Lumefantrine Artesunate + mefloquine Dihydroartemisinin + piperazine
Complicated <i>P. falciparum</i> malaria	Artesunate IV OR Artemether Im or Quinine IV
Radical Treatment of <i>P. vivax</i> and <i>P. ovale</i>	Primaquine

ANTI-AMEBIC DRUGS

Tissue Amebicidases	Luminal Amebicidases
Intestinal and Extra-Intestinal amebicides	<ul style="list-style-type: none"> Diloxanide furoate Iodoquinol (Di-iodo-hydroxyquin) Tetracyclines, Paromomycin
<ul style="list-style-type: none"> Metronidazole, tinidazole, ornidazole, secnidazole Emetine, dihydroemetine (highly toxic - NOT used now) Nitazoxanide 	
Extra-Intestinal amebicide	
<ul style="list-style-type: none"> Chloroquine 	

Metronidazole and Analogs

- MOA: Reduced metronidazole is toxic to **anaerobic bacteria and protozoa** and disrupts replication transcription and repair process of DNA.
- It is **DOC for extraintestinal amebiasis**.
- Highly effective for *trichomoniasis*, *giardiasis*, *clostridium difficile* associated *pseudomembranous colitis*.
- Adverse effects: Vomiting, **metallic taste**.
- Tinidazole and Ornidazole are better tolerated.
- Secnidazole is used a **single dose** 2g for amebiasis, giardiasis and trichomoniasis.

ENDOCRINE SYSTEM

Growth Hormone (GH) Related Drugs

- Octreotide**: Long acting **analog of somatostatin**; **41 times more potent** than somatostatin in inhibiting GH release. **Uses include**
 - GH secreting pituitary tumors/acromegaly.
 - Also controls symptoms in carcinoid syndrome, VIP secreting tumors; gastrinoma.
 - Secretory diarrhea caused by diabetes and irritable bowel syndrome.
 - Controlling bleeding from esophageal varices, bleeding peptic ulcers.
- Lanreotide** is similar to octreotide but used for treating **thyroid tumors**.
- Pegvisomant**: **GH receptor antagonist** for treating acromegaly.
- Recombinant human growth hormone (HGH) **Somatropin and Somatrem** - used for treating GH deficiency.
- Mecasermin**: **recombinant IGF-1** + recombinant IGFBP-3 for treating **short stature**.

Drugs for Hyperprolactinemia

- Dopamine agonist** drugs
 - Bromocriptine
 - Carbexoline
 - Pergolide
 - Quinagolide

Steroids related points

- Dexamethasone** - **most potent** glucocorticoid.
- Deflazacort** is a newly introduced glucocorticoid which has similar efficacy to prednisone but lesser side effects.
- Glucocorticoid synthesis Inhibitors**: Metyrapone, Aminoglutethimide; Mitotane; Trilostane; Ketoconazole; Abiraterone.

- Glucocorticoid antagonists: **Mifepristone**
- Mineralocorticoid antagonists: Spironolactone; Eplerenone.
- Anabolic steroids** (testosterone derivatives) were developed to reduce virilising effects while maintaining the anabolic effects: Methandienone; Oxymetholone; Nandrolone, Stanozolol.

Classification of Thyroid Inhibitors

- Inhibit hormone synthesis** (Antithyroid drugs)

- Propylthiouracil** (favored during pregnancy and breastfeeding), **methimazole**, **carbimazole**
- Inhibit iodide trapping** (Ionic inhibitors)
 - Thiocyanates, perchlorates, nitrates
- Inhibit hormone release**
 - Iodine, iodides of Na and K, organic iodide
- Destroy thyroid tissue**
 - Radioactive iodine (131I, 125I, 123I)
- Drugs causing hypothyroidism/goiter** as a side effect:
 - Lithium**; **Amiodarone**; **Sulfonamides**, paraaminosalicylic acid; Phenobarbitone, phenytoin, carbamazepine, rifampin.

DRUGS FOR DIABETES MELLITUS

INSULIN

- Discovered in 1921 by **Banting and Best**.
- The **Nobel Prize in Physiology or Medicine 1923** was awarded jointly to **Frederick Grant Banting and John James Rickard Macleod** "for the discovery of insulin".
- Secretion and structure of insulin:
 - Insulin is produced in the **beta cells of the pancreatic islets**.
 - It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, **preproinsulin**.
 - Subsequent proteolytic processing removes the amino-terminal signal peptide, giving rise to **proinsulin**.
 - Cleavage of an internal 31-residue fragment from proinsulin generates the **C peptide (connecting peptide)** and the **A (21 amino acids) and B (30 amino acids) chains** of insulin, which are connected by **two disulfide bonds**.
 - The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells.
- Other insulins**: **Pork insulin** differs from human insulin by 1 amino acid, **beef insulin** by 3 amino acids. "Pig (pork) is smaller (=1) than, cow (beef) (=3)".
- Importance of C peptide**: C peptide is secreted in the blood along with insulin. Thus in insulinoma, C peptide levels should parallel plasma insulin values. However in iatrogenic hypoglycemia, due to exogenous insulin injection, there is a high plasma insulin level with low C peptide level. Sulfonylureas elevate the concentration of both C peptide and insulin in the plasma. Therefore, iatrogenic hypoglycemia due to oral hypoglycemics can

only be diagnosed by a high index of suspicion coupled with assay of drug in plasma or urine.

- Regulation**:
 - Somatostatin inhibits release of both insulin and glucagon.
 - Glucagon evokes release of insulin as well as somatostatin. Insulin inhibits glucagon secretion.
- Insulin receptor**: is a **cell membrane receptor**, a heterotetrameric glycoprotein consisting of 2α and 2β subunits linked by disulfide bonds; the β subunit has tyrosine kinase activity.
- Recombinant human insulin** is made by **cDNA**.

Glucagon-like Peptide-1

- GLP-1 is the **most potent incretin** derived from the transcription product of the proglucagon gene.
- The major source of GLP-1 in the body is the **intestinal L cell** that secretes GLP-1 as a gut hormone.
- After a carbohydrate rich meal** insulin secretion is stimulated by **GLP-1**.
- Hormone that **remain stable with aging** is GLP-1.

Insulin Resistance

- Insulin resistance is said to have occurred **when more than 100 units** of insulin is needed to keep the blood glucose level within normal limits.
- Causes of insulin resistance "**LOW PRACs**"
 - Leprechaunism**; **Lipodystrophy** states (partial or generalized); **Obesity** (MC cause); **Werner's syndrome**; **Pregnancy**; **Polycystic ovaries**; **Pineal hyperplasia syndrome**; **Rabson Mendenhall syndrome**; **Acute and chronic Renal failure**; **Anti-insulin Antibodies**; **Acromegaly**; **Asian origin**; **Alstrom syndrome**; **Ataxia telangiectasia**; **Cystic fibrosis**.

Clinical Markers of Insulin Resistance

- **Acanthosis nigricans**
- Multiple skin tags (**acrochordons**)
- **Acromegaloïd** features
- **Hyperandrogenism** (acne, hirsutism, oligomenorrhea)
- Central obesity and **high waist: hip** ratio
- **High** Body mass index (BMI) > 30 kg/m².

Summary of Insulins

- **Prandial (Bolus) Insulins:** They *mimic pancreatic beta cell secretion* of insulin in response to meal load;

they *act rapidly* (10-20 min), peak at 1 hour and have a duration of action of 3-4 hours. They are called "bolus" since all are administered (SC or inhalational) 30 min prior to the first bolus of the meal to control the postprandial hyperglycemia.

- **Basal insulins** include both *intermediate and long acting* insulins. NPH is mentioned in some textbooks as long acting. Their duration of action is 12-16 hours - thus they are administered twice daily and provide consistent levels of insulin throughout the day.
- **Premixed insulin** preparations with long acting + short acting preparations are available and used twice daily

	Source	Comments
PRANDIAL (BOLUS) INSULINS		
Ultrashort (Rapid/Fast) Acting Insulins		
Insulin Lispro	Human modified Analog	Clear Solutions; pH 7.4; given SC; can be mixed with NPH insulin
Insulin Aspart		Clear Solutions; pH 7.4; given SC; can be given IV; can be mixed with NPH insulin
Insulin Glulisine		Clear Solutions; pH 7.4; given SC; can be mixed with NPH insulin
Inhaled Insulin	Human Insulin	Liquid human insulin filled cartridges are available for loading on the electronic inhalation device
Short Acting Insulin		
Regular Insulin (Crystalline Zinc Insulin)	Human or Pork Insulin	Clear Solution; given SC/IV; can be mixed with all types of insulins except long acting insulins
BASAL INSULINS		
Intermediate Acting Insulins		
NPH or Isophane insulin	Human or Pork modified by protamine	Cloudy solution; give SC only; NOT IV; can be mixed with ultrashort acting and regular insulins
Long Acting Insulins		
Insulin Glargine	Human modified Analog	Clear solution at pH 4; given SC only (NOT IV); should NOT be mixed with other insulins
Insulin Detemir		Clear solution at pH 4; given SC only (NOT IV); should NOT be mixed with other insulins; LOWER risk of nocturnal hypoglycemia
Insulin Degludec		Clear solution at pH 7.4; given SC only (NOT IV); should NOT be mixed with other insulins; LOWER risk of nocturnal hypoglycemia

EXTRA EDGE

- Mnemonic: **L**ispro, **A**spart, **G**lulisine are rapidly acting -i.e, there is no **LAG!**
- **NPH** = Insulin with **N**eutral pH, conjugates with **P**rotamine (found in fish sperms) and was developed by **H**agedorn.
- **Isophane insulin** is that NPH insulin which has **6 molecules** of insulin per molecule of protamine.
- **Cloudy** insulin is **NPH insulin**.
- Long acting insulins are **NOT** mixed with other Insulins.
- Inhaled, regular and NPH insulin are **human insulins**; others are **recombinant insulin analogs**.
- **Lente** Insulin (insulin zinc suspension with amorphous + crystalline insulin particles) was an intermediate acting insulin; **Ultraente** (extended insulin zinc suspension with crystalline insulin particles) was a long acting insulin - both had high variability in absorption and hence **declined in usage**.

Inhaled Insulin (Afrezza)

- Used for **both** type 1 and type 2 diabetes mellitus.
- Approved for **treatment of only postprandial hyperglycemia** prior to meals.
- For **maintenance basal insulin** is also given at loading dose along with afrezza.
- Used **30 minutes before** the meal.
- Given by an electronic device that senses and releases insulin when inhalational velocity is maximum.
- Can administer insulin in **1 unit increments**; Use and throw colour coded cartridges of afrezza are available with **4, 8 and 12 units** of insulin
- Absorption is rapid with peak plasma insulin level reaching within 15 minutes and then declines to baseline after 3 hours.
- MC side-effect is **cough** and few cases of lung cancer has also been seen in trials.
- It is **contraindicated in smokers** and patients of **asthma and COPD**.

NEWER IMMUNOSUPPRESSANT DRUGS

Metabolic Actions of Insulin and Glucagon

Functions of insulin Anabolic effects	Functions of glucagon Catabolic effects
↑ Glucose transport (muscle, adipose tissue)	↑ Glycogenolysis
↑ Glycogenesis (glycogen synthesis and storage)	↑ Gluconeogenesis
↑ Glycolysis	↑ Ketogenesis
↑ Lipogenesis (triglyceride synthesis and cholesterol synthesis)	↑ Lipolysis
↑ protein synthesis	
↑ sodium retention (kidneys)	
↑ cellular uptake of K ⁺	
" L-BRICK " (don't need insulin for glucose uptake) = Liver, Brain, RBCs, Intestine, Cornea, Kidneys	

GLUT (Glucose Transporters)

- GLUTs mediate facilitated diffusion of glucose across cell membranes:
 - GLUT 1: brain, colon, kidney, RBCs
 - GLUT 2: liver, pancreatic beta cells
 - GLUT 3: brain, kidney, placenta
 - GLUT 4: heart, skeletal muscle, adipose tissue - the ONLY insulin responsive glucose transporter
 - GLUT 5: small intestine.
- After an **overnight fast**, level of **GLUT receptors** is **decreased in adipocytes**.

ORAL HYPOGLYCEMIC DRUGS

Drug	Mechanism	Adverse Effects
Enhance Insulin secretion		
Sulfonylureas (K-ATP channel blockers) Gen I: chlorpropamide, tolbutamide Gen II: glyburide, glipizide, glimepiride, gliclazide	↑ insulin secretion from β-islet cells	GI: disulfiram-like effects GI: Hypoglycemia ; CI in hepatic or renal insufficiency
Meglitinides/phenylalanine analogues Repaglinide, Nateglinide, Mitiglinide	↑ insulin secretion from β-islet cells	Hypoglycemia ; significantly more expensive than sulfonylureas with no therapeutic advantage
Glucagon-like peptide-1 (GLP-1) agonists Exenatide, Liraglutide, dulaglutide, Lixisenatide	↑ insulin secretion , ↓ glucagon, slow gastric emptying, satiety,	
Dipeptidyl peptidase (DPP-4) inhibitors Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin, Linaclotide - " gliptins ".	↑ insulin secretion , Prolong endogenous GLP-1 action	Nasopharyngitis
Overcome insulin resistance		
Biguanides (AMPK, AMP activated Protein Kinase activator) Metformin	↓ hepatic gluconeogenesis , ↑ glycolysis, ↑ Insulin activity and ↓ insulin resistance, ↓ hyperlipidemia	Lactic acidosis , Diarrhea , metallic taste, ↓ vitamin B ₁₂ absorption; CI in hepatic and renal insufficiency
Thiazolidinediones (PPAR, Peroxisome proliferator activated receptor-gamma activator) Pioglitazone	↓ hepatic gluconeogenesis, ↑ tissue uptake of glucose, ↓ Insulin resistance	Weight gain, anemia, pedal edema , CHF, ↑ serum LDL, macular edema, hepatotoxicity; Safer in renal disease CI in liver disease, CHF (Rosiglitazone banned due to MI)
Miscellaneous antidiabetic drugs		

Contd...

Contd...

Drug	Mechanism	Adverse Effects
<i>α-Glucosidase Inhibitors</i> Acarbose, Miglitol, Voglibose	Inhibit intestinal brush border α-glucosidases → (↓ intestinal glucose absorption)	Flatulence, Diarrhea, GI disturbance
<i>Amylin analogue</i> Pramlintide	↓ glucagon, slow gastric emptying	Hypoglycemia, nausea, diarrhea
<i>Sodium glucose cotransporter-2 Inhibitors (SGLT-2)</i> Canagliflozin, Dapagliflozin, Empagliflozin	Inhibition of SGLT-2 in proximal convoluted tubules causes ↑ urinary glucose excretion (glycosuria)	Glycosuria
<i>Dual PPAR agonist</i> Saroglitazar	Agonist action at PPAR alpha lowers high blood triglycerides , and agonist action on PPAR gamma - ↓ insulin resistance	
<i>Dopamine D2 agonists</i> Bromocriptine	↓ Insulin resistance	

EXTRA EDGE

- From above table it is clear that, **agents which increase insulin secretion** are: sulfonylureas, meglitinides ("~glinides"); GLP-1 agonists (exenatide, etc.) and DDP-IV inhibitors ("~gliptins").
- Insulin, Exenatide and pramlintide are **parenteral preparations**.
- Epalrestat: Aldase reductase Inhibitor** that has been found to **delay sorbitol** accumulation in sciatic and other nerves and hence **delays progression of diabetic neuropathy**.

More Diabetes related High Yield

- Measurement of **glycated hemoglobin (HbA1c)** is the standard method for assessing **long-term glycemic control** - it reflects the glycemic history over the previous **2-3 months**, because erythrocytes have an average life span of **120 days**.
- In adults with diabetes **HbA1c should be < 7%**.
- Amylin** is a 37-amino-acid peptide cosecreted with insulin from pancreatic beta cells.
- The **microvascular complications** of both type 1 and type 2 DM result from **chronic hyperglycemia**.
- The appearance of **neovascularization** in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy.
- Diabetic nephropathy** is the leading cause of chronic kidney disease (CKD), End Stage Renal Disease, and CKD requiring renal replacement therapy.

- The **MC** form of **diabetic neuropathy** is **distal symmetric polyneuropathy**.
- The **MC skin** manifestations of DM are **xerosis and pruritus** and are usually relieved by skin moisturizer.

Drug Class	Examples
MOA: inhibitors of lymphocyte signaling to prevent immune cell activation and proliferation	
Calcineurin Inhibitors	Cyclosporine, tacrolimus
mTOR inhibitors	Sirolimus, Everolimus, Zotarolimus
MOA: Cytokine and Cytokine receptor abnormalities	
TNF-Alpha Inhibitors	Etanercept; Infliximab; Adalimumab; Certolizumab; Golimumab
IL-1 receptor antibodies	Anakinra, Rilonacept, canakinumab
IL-2 receptor antibodies	Daclizumab, Basiliximab
IL-6 receptor antibodies	Tocilizumab
IL-12/IL-23 p40 Cytokine inhibitors	Ustekinumab
IL-17 receptor antibodies	Ixekizumab; Secukinumab, Brodalumab
Monoclonal Antibodies (Mab) against specific immune molecules	
Anti CD 52	Alemtuzumab
Anti-CD3 (OKT3)	Muromomab
Anti-IgE antibody	Omalizumab
Anti-IL5	Reslizumab
Anti-CD 20	Rituximab
Anti-CD 25	Basiliximab
B-lymphocyte stimulator (BLS) cytokine inhibitor	Bellmumab
Antibody-drug conjugate	Brentuximab vedotin
LFA-3 (CD-58) Inhibitor	Alefacept
Inhibitors of Immune cell adhesion and activation	
Anti LFA-1/FA-3 Mab	Efalizumab, Alefacept
Alpha-4 Integrin inhibitor	Natalizumab
Inhibitors of Immune cell costimulation in Induced anergy (Tolerogens)	
Anti-CD 80/ CD 86 Mab	Abatacept, belatacept
CTLA-4 inhibitor	Ipilimumab
PD-1 Inhibitor	Nivolumab; Pembrolizumab

GENE TRANSFER/GENE THERAPY

- In Gene transfer/therapy, the active agent is a nucleic acid rather than a protein or small molecule.
- Because delivery of naked DNA or RNA to a cell is an inefficient process, **most gene transfer is carried out using a vector** (gene delivery vehicle).
- Vectors have been engineered from viruses **by deleting some or all of the viral genome and replacing it with the therapeutic gene** of interest under the control of a suitable **promoter**.
- Gene transfer strategies involves: (1) a vector; (2) a gene to be delivered, sometimes called the **transgene**; and (3) a relevant target cell to which the DNA or RNA is delivered.
- The series of steps in which the donated DNA enters the target cell and expresses the transgene is referred to as **transduction**.

Gene Transfer Methods

Non-Viral Methods	Viral methods (viruses)
<ul style="list-style-type: none"> Physical Electroporation Microinjection Direct injection of DNA Gene particle bombardment 	<ul style="list-style-type: none"> Chemical Liposome mediated Calcium phosphate coprecipitation Ligand-DNA conjugates DEAE dextran Polybrene Retrovirus Adenovirus Adeno-associated virus Lentivirus Human Foamy Virus HSV-1 SV-40 (sarcoma virus 40)

EXTRA EDGE

One form of **Leber's Congenital Amaurosis**, patients with has been **successfully treated by gene therapy** in clinical trials.

Potential Complications of Gene Therapy

- Gene silencing:** Repression of promoter
- Genotoxicity:** Complications arising from insertional mutagenesis
- Phenotoxicity:** Complications arising from overexpression or ectopic expression of the transgene
- Immunotoxicity:** Harmful immune response to either the vector or transgene
- Risks of horizontal transmission: Shedding of infectious vector into environment
- Risks of vertical transmission: Germline transmission of donated DNA.

Diseases Treated by Gene Therapy

- SCID - Severe Combined Immunodeficiency
- ADA - Adenosine Deaminase Deficiency
- Lipoprotein lipase deficiency
- X-linked adrenoleukodystrophy
- Metachromatic leukodystrophy
- Wiskott Aldrich syndrome
- Hemophilia B
- Beta thalassemia
- Leber's congenital amaurosis (**LCA2** bearing a mutation in the **RPE65 gene**).

EXTRA EDGE

- Luxturno (Voretigene neparvovecrzyf)** is a **adeno-associated virus (AAV)** vector based gene therapy used for treatment of patients with inherited retinal disease due to mutations in both copies of the **RPE65 gene** which can only be confirmed through genetic testing.

"-OMics"

- Epigenomics:** is the study of alterations in chromatin and histone proteins and methylation of DNA sequences that influence gene expression.
- Proteomics:** The study of the entire library of proteins made in a cell or organ and its relationship to disease.
- Microbiomics** is the study of the bacterial flora of a person.
- Metagenomics**, of which microbiomics is a part, is the genomic study of environmental species that have the potential to influence human biology directly or indirectly. EX: *study of exposures to microorganisms in farm environments that might be responsible for the lower incidence of asthma among farm-raised children.*
- Metabolomics** is the study of the range of metabolites in cells or organs and the ways they are altered in disease states.

ANTICANCER DRUGS**Chemotherapy Terms**

- Neoadjuvant chemotherapy** consists of giving antineoplastic drugs in advance of surgery or radiation therapy—doubtful use.
- Adjuvant chemotherapy** consists of administering antineoplastic drugs following surgery or radiation therapy—used in stage 1A and above.

ALKYLATING AGENTS

Mechanism of action (MOA): They produce highly reactive *carbonium ion intermediates* that *transfer alkyl*

groups to *N-7 or O-6 of guanine of DNA*. This results in *DNA cross-linking, abnormal base pairing and breaking of DNA strand*.

Classic nitrogen mustards	
Drug	Details
Mechlorethamine (Mustine HCl)	First nitrogen mustord; highly reactive and local vesicant, can be given only by IV route; topical use in cutaneous lymphoma Severe vesicant
Cyclophosphamide	A prodrug that is transformed into active metabolites (phosphor amide mustard and acrolein) Hemorrhagic cystitis (due to acrolein; protected by "mesna"), very high doses cause acute myocardial necrosis, alopecia, SIADH
Ifosfamide (analog of cyclophosphamide)	It is always given with mesna to prevent hemorrhagic cystitis, A reversible neurotoxicity. Manifested primarily as altered mental status.

EXTRA EDGE

Nitrogen Mustards are also called *Radiomimetic* drugs since their actions resemble ionizing radiation to some extent.

Nitrosoureas	
Drug	Details
Nitrosoureas (Carmustine, Lomustine, Semustine, bendamustine, Estramustine)	Highly lipid soluble (crosses blood brain barrier) with excellent penetration into the CNS; used for treating brain tumors. Renal damage (with semustine), leukemogenic; CNS toxic (dizziness, ataxia); Gynecomastia and thromboembolism (estramustine)

Platinum compounds	
Drug	Details
Cisplatin	Platinum compound; highly emetic (maximum among all anti-cancer drugs) Nephrotoxicity (proximal and distal tubule cells); Ototoxic (high frequency hearing loss); neurotoxicity (sensory neuropathy)
Carboplatin	A II generation platinum compound Same as cisplatin but milder, but more myelosuppressive
Oxaliplatin	Acute and chronic neurotoxicity, reversible laryngopharyngeal spasm

Triazines	
Drug	Details
Dacarbazine	It differs from other alkylating agents in having primary inhibitory action on RNA and protein synthesis (others mainly affect DNA)

Contd...

Triazines	
Procarbazine	Causes MAO inhibition; Disulfiram like reaction with alcohol;
Temozolomide	Headache, constipation
Others	
Drug	Details
Busulfan	Specific for myeloid elements granulocyte precursors being most sensitive Hyperpigmentation, pulmonary fibrosis, hyperuricemia, sterility, adrenal insufficiency
Chlorambucil	Very slow acting, specifically active on lymphoid tissue, myeloid tissue is largely spared

ANTIMETABOLITES

Folate Antagonist	
Drug	Details
Methotrexate (MTX)	S-phase specific; inhibits the enzyme dihydrofolate reductase → ↓ dTMP and therefore DNA and protein synthesis (pseudoreversible inhibition). Folinic acid (leucovorin, citrovorum factor) rescue for doses over 100 mg/m2. BMS, mucositis, acute renal failure, idiosyncratic pneumonitis, hepatotoxicity (microvesicular fatty change), rash, ↑ toxicity when effusions (pleural effusion, ascites) are present; transient reversible oligospermia; in extreme MTX toxicity

Contd..

Contd

Folate Antagonist	
	Glucopridose—an MTX cleaving enzyme maybe used. SE with intrathecal MTX: orochneiditis; neurotoxicity and necrotising demyelinating leukoencephalopathy
Pemetrexed	Mainly targets thymidylate synthetase; causes hand-foot syndrome; Folate/B12 supplementation required

Purine Antagonists	
Drug	Details
Mercaptopurine (6-MP); Thioguanine (6-TG)	Blocks de novo purine synthesis; require activation by HGPRT (hypoxanthine-guanine-phosphoribosyl transferase) before they can inhibit purine biosynthesis. reversible cholestatic jaundice; 6-MP is metabolized by xanthine oxidase; its metabolism is ↓ by allopurinol (xanthine oxidase inhibitor), ↓ dose if allopurinol is given concurrently
Arathioprine	Precursor of 6-MP that interferes with metabolism and synthesis of nucleic acids. Toxic to proliferating lymphocytes; toxic effects ↑ by allopurinol
Fludariabine	Fluorinated derivative of antiviral, vidarabine; it is phosphorylated by deoxycytidine kinase before being incorporated into DNA and inhibiting DNA synthesis
Cladribine (chlorodeoxyadenosine)	Phosphorylated by deoxycytidine kinase → gets incorporated into DNA → inhibits DNA polymerase and DNA replication DOC for hairy cell leukaemia
Pentostatin (deoxy-coformycin)	Irreversible inhibitor of the enzyme adenosine deaminase; Also used to treat hairy cell leukemia

ANTIMICROTUBULES

Vinca Alkaloids	
Drug	Details
Vincristine (from periwinkle plant Catharanthus roseus)	M-phase specific alkaloids that bind to tubulin and block polymerization of microtubules so that mitotic spindle cannot form; chromosome fails to move apart during metaphase (arrest)—'spindle poisons' Neurotoxic (areflexia, peripheral neuropathy, SIADH) and alopecia
Vinblastine	Similar to above
Vinorelbine	Similar to above

Taxanes	
Drug	Details
Paclitaxel and docetaxel, Cabazitaxel	They function by stabilizing microtubules and preventing their disassembly – anaphase cannot occur Peripheral neuropathy (glove and stocking),

Epothilones	
Drug	Details
Ixabepilone	Myelosuppression and peripheral neuropathy; used in Breast Ca resistant to taxanes and anthracyclines

ENZYME INHIBITORS: TOPOISOMERASE INHIBITORS

Drug	Details
Topotecan, Irinotecan (from tree camptotheca acuminata)	Inhibitor of topoisomerase I. Cholinergic effects (by irinotecan)
Etoposide	Arrests cells in the G2 phase and causes DNA breaks by stimulating DNA topoisomerase II

ANTITUMOR ANTIBIOTICS

Drug	Details
Doxorubicin, Daunorubicin, Idarubicin, Epirubicin, (Anthracyclines)	Generate free radicals and non-covalently intercalate in DNA (creating breaks in DNA strand to ↓ replication) Cardiotoxicity; can be prevented by dexrazoxone; anthracyclines also cause radiation recall effect
Dactinomycin (Actinomycin D)	It intercalates between DNA base pairs and unwinds the DNA helix Radiation recall
Bleomycin	Chelates copper or iron, produces superoxide ions, free radicals and intercalates between DNA strands – causes chain scission and inhibits DNA repair. Causes Pulmonary fibrosis (hyperplasia of type II pneumocytes), earliest indicator is decreased DLCO. Oxygen enhances pulmonary toxicity

Contd...

Contd...

Drug	Details
Mitomycin C	Activated intracellularly and then cross links DNA ; active at sites of low oxygen tension (a bioreductive drug) can cause hemolytic uremic syndrome
Mitoxantrone	Analogue of doxorubicin

MISCELLANEOUS AGENTS

Drug	Mechanism of action
Procarbazine	After oxidation by hepatic enzymes depolymerises DNA and causes chromosomal damage; also inhibits nucleic acid synthesis
L-asparaginase	The enzyme L-asparaginase (from E.coli) degrades L-asparagine to L-aspartic acid depriving leukemic cells of an essential metabolite – may cause cell death
Hydroxyurea	Inhibits ribonucleotide reductase - ↓ DNA synthesis

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Drug	Mechanism of action
Tamoxifen, Raloxifene, Toremifene	Receptor antagonists In breast, agonists in bone; block the binding of estrogen to estrogen receptor positive cells ↑ risk of endometrial Ca ; hot flashes; raloxifene DOES NOT cause endometrial Ca since it is an endometrial antagonist

TARGETED THERAPY: TYROSINE KINASE INHIBITORS

Drug	Disease	MOA
Imatinib (Gleevec); Dasatinib, Nilotinib, Ponatinib, Bosutinib	Chronic Myeloid Leukemia, GIST	Blocks ATP binding to tyrosine kinase active site Blocks the ability of mutant BCR-ABL fusion protein to bind ATP Inhibition of mutant c-KIT
Sunitinib	GIST; renal cell cancer (RCC)	Inhibits activated c-Kit and PDGFR in GIST; inhibits VEGFR in RCC

Contd...

Contd...

Drug	Disease	MOA
Sarafenib	RCC; hepatocellular carcinoma	Targets VEGFR pathways in RCC Possible activity against BRAF in melanoma, colon cancer, and others
Regorafenib	Colorectal cancer; GIST	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases

Drug	Disease	MOA
Erlotinib	Non-small cell lung cancer; pancreatic cancer	Competitive inhibitor of the ATP-binding site of the EGFR
Gefitinib	Non-small cell lung cancer	Inhibitor of EGFR tyrosine kinase
Axitinib	RCC	Competitive inhibitor of ATP binding site of tyrosine kinase domain VEGF receptors
Crizotinib	Non-small-cell lung cancer	Inhibitor of ALK tyrosine kinase
Cabozantinib, Vandetanib	MTC	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Ruxolitinib	Myelofibrosis	Competitive inhibitor of tyrosine kinase
Lapatinib	HER-2/neu positive breast cancer refractory to trastuzumab given in combination with capecitabine	Inhibitor of HER-2/ neu and EGFR. It may also prevent brain metastases
Afatinib	Non small cell Lung ca	

KEY: (PDGF) Platelet-derived growth factor; (EGF) Epidermal growth factor; (GIST) Gastrointestinal Stromal Tumor; (VEGF) Vascular endothelial growth factor; (RCC) Renal cell carcinoma; (MTC) Medullary Thyroid carcinoma.

TARGETED THERAPY: MONOCLONAL ANTIBODIES

Drug	Disease	MOA
Trastuzumab (Herceptin), Pertuzumab	Breast Ca	Binds HER2/neu (acts against erb-B2) on tumor cell surface and induces receptor internalization; Combination with anthracyclines = increased cardiotoxicity

Contd

Contd

Drug	Disease	MOA
Cetuximab	Colon Ca, squamous cell Ca of the head and neck (Used with concurrent radiotherapy)	Binds extracellular domain of EGFR and blocks binding of EGF and TGF; Induces receptor internalization; potentiates effect of chemotherapy and radiotherapy
Panitumumab	Colon Ca	Like cetuximab above
Nilutimab	B cell lymphomas and leukemias that express CD20	Multiple potential mechanisms, including direct induction of tumor cell apoptosis and immune mechanisms
Alemtuzumab	Chronic lymphocytic leukemia and CD52 -expressing lymphoid tumors	Immune mechanisms
Bevacizumab	Colon, lung, breast Ca; diabetic retinopathy, CRVO etc.	Inhibits angiogenesis by high-affinity binding to VEGF
Ipilimumab	Melanoma	Blocks CTLA-4 , preventing interaction with CD80/86 and T cell inhibition
Pembrolizumab	Melanoma	Blocks Phosphodiesterase-1 (PD-1) preventing interaction with PD-L1 T cell inhibition

Radio-isotope Carrying mAbs

• **Ibritumomab tiuxetan** is an **yttrium-90-labeled antibody to CD20** that is approved for the treatment of **low-grade non-Hodgkin lymphoma refractory to rituximab or transformed B cell non-Hodgkin lymphoma** – the first targeted **radioimmunotherapy** approved for clinical use. **Tositumomab** linked to **I-131** is similar but dosimetry is required and use is cumbersome.

Toxin-linked mAbs

• **Cemtuzumab, ozogamicin** is an **antibody to CD33 linked to a potent antitumor antibiotic, calicheamicin+**

that is approved for the treatment of patients > 60 years with relapsed or **refractory AML**. This is the first example of antibody-targeted chemotherapy used clinically.

Retinoids

- **Tretinoin**: Targets a specific fusion protein caused by a chromosomal translocation. This oral agent induces differentiation and decreased proliferation without cytotoxicity of **acute promyelocytic leukemia** cells (APML, AML M3). SE: **Retinoic acid syndrome** (fever, dyspnoea, pleural or pericardial effusion) must be treated emergently with **dexamethasone**; headache; dry skin; rash; flushing.
- **Bexarotene**, a retinoid that selectively **activates the retinoid X receptor (RXR)**, is approved to treat **cutaneous T cell lymphomas (mycosis fungoides)**.

Histone Deacetylase Inhibitors

Vorinostat and Romidepsin: Are **HDAC (Histone DeAcetylase) inhibitor** to be approved for the treatment of **cutaneous T-cell lymphoma** progressing after two systemic therapies.

mTOR Inhibitors

(Mammalian Target of Rapamycin)

- **Temsirolimus** is a **derivative of rapamycin**, an immunosuppressive agent, and **blocks the effects of mTOR**. mTOR has an important role in regulating synthesis of the proteins that regulate cell division; blocking mTOR reduces cancer cell proliferation, approved for the treatment of **advanced renal cell carcinoma**.
- **Everolimus**: Used in RCC, breast cancer.

Targeted Toxins

- **Denilekin difitox**: a recombinant DNA-derived cytotoxic protein composed of **amino acid sequences for diphtheria toxin fragments** followed by the sequences for **IL-2**. This **fusion protein** was designed to direct the cytotoxic action of diphtheria toxin to cells that express the **IL-2 receptor**, such as the tumor cells in **cutaneous cell lymphoma (mycosis fungoides)**. SE: hypersensitivity and delayed **vascular leak syndrome** (pulmonary and peripheral edema).

Biological Response Modifiers

- **Interferon alpha:** recombinant interferon alpha has marked anti-tumor activity in hairy cell leukaemia and CML, moderate effects in lymphomas. In the epidemic (AIDS-associated) form of Kaposi's sarcoma, in multiple myeloma, and as adjuvant therapy for malignant melanoma.
- **Aldesleukin (IL-2):** It is a recombinant interleukin 2 (IL-2), used in the treatment of metastatic renal cell Ca and melanoma. Given by slow IV infusion or subcutaneously. Most of the life-threatening toxicities of aldesleukin are due to a 'capillary leak syndrome'.

Serine Threonine Kinase Inhibitors

- **Vemurafenib, dabrafenib** (targets BRAF) and **Trametinib** (targets MEK) - all used in melanoma treatment.

Proteasome Inhibitors

- **Bortezomib, Carfilzomib:** Interferes with proteasomal degradation of regulatory proteins; in particular, prevents NF kappa B from preventing apoptosis; used in Multiple myeloma; causes neuropathy.

Antibody-Chemotherapy Conjugates

- **Brentuximab vedotin:** Delivery of chemotherapeutic agent (MMAE, monomethyl auristatin E) to CD30-expressing tumor cells; used in Hodgkin's disease and anaplastic lymphoma.
- **Ado-trastuzumab emtansine:** Delivery of chemotherapeutic agent emtansine to HER2-expressing breast cancer cells.

More High Yield Points

- **Thalidomide:** Combination of thalidomide with dexamethasone results in enhanced responses—used in advanced and relapsed multiple myeloma. SE: rashes, somnolence, and constipation.
- **Revlimid:** Belongs to a new class of more potent and less toxic immunomodulatory drugs or **ImiDs**, which are believed to affect multiple pathways within the cell and inhibit TNF-α and is now approved for the treatment of transfusion-dependent myelodysplasia.
- **Sipuleucel-T:** Is approved for use in patients with hormone-independent prostate cancer. It consists of purified antigen presenting cells.
- **All-trans retinoic acid:** Inhibits transcriptional repression by PML-RAR alpha; used in APL M3 t(15;17).

- **Arsenic trioxide:** indicated both for induction in remission and for consolidation in relapsed or refractory APL (AML M3).
- **Lonafamib** and **tipafamib:** Inhibition of farnesyl transferase and consequent inactivation of ras-dependent signal transduction; used in leukemia treatment.
- **Vismodegib:** Target smoothened receptor in hedgehog pathway; for treating metastatic basal cell Ca.
- **Side effects of Bevacizumab (Avastin):** Side effects: hypertension (MC); Proteinuria, thromboembolism, gastrointestinal perforation, wound dehiscence, hemoptysis (lung cancer), reversible posterior leukoencephalopathy syndrome (RPLS), tracheo-esophageal fistula.
- **Side effects of Sorafenib:** Hypertension, hand-foot syndrome.

Cell Cycle-Specific Anticancer Drugs

- **G1:** Vinblastine
- **S:** MTX, Mitomycin C, Doxorubicin, Cytarabine, Hydroxyurea, Daunorubicin, 6-MP, 6-TG, 5-FU. ("My Miser Didn't Clear His Debt." 665. Rs.!!!)
- **G2:** Daunorubicin, Bleomycin, Etoposide, Topotecan
- **M:** Vincristine, Vinblastine, Paclitaxel, Docetaxel.

SUPPORTIVE AGENTS

Allopurinol	Prevents hyperuricemia from tumor lysis syndrome
Rasburicase	Prevent hyperuricemia from tumor lysis syndrome
Mesna	Prevents ifosfamide bladder toxicity
Leucovorin	Protects against methotrexate toxicity to normal cells
Amlifostine	Prevents radiation toxicity
Dexrazoxane	Protects against anthracycline cardiac toxicity
Palifermin	(Prevents mucositis); keratinocyte growth factor inhibitor
Pilocarpine hydrochloride	Ameliorate dry mouth from radiation
Pamidronate, Zoledronic acid	Treat hypercalcemia, reduce effects of bone metastases
Denosumab	RANK ligand inhibitor; reduce effects of bone metastases; used to treat osteoporosis
Samarium and Strontium	Reduce Pain from bone metastasis
Dexrazoxane	A chelating agent, a cyclic derivative of EDTA that may prevent anthracycline-induced cardiomyopathy.

Contd.,

Anti

Amlifostine

Cytoprotective agent, prevents radiation toxicity. MOA: It is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. The higher concentration of free thiol in normal tissues is available to bind to and thereby detoxify reactive metabolites of cisplatin. Free thiol may also act as a scavenger of free radicals that may be generated in tissues exposed to cisplatin.

CANCER CHEMOTHERAPY COMPLICATIONS

Cancer Chemotherapy-induced Bone Marrow Suppression (Myelosuppression)

Anemia

- Treatment: Erythropoietin stimulating agents: **Epoetin alfa** (erythropoietin) and **Darbepoetin alfa** (Long-acting erythropoietin);
- Increased risk of thromboembolism; patients should be iron replete before starting treatment; HTN MUST be controlled.

Neutropenia

- **Febrile neutropenia** prophylaxis: **Filgrastim:** G-CSF, granulocyte colony stimulating factor; **Sargramostim:** GM-CSF, granulocyte-macrophage colony stimulating factor (- also for myeloid reconstitution following bone marrow transplant)

Thrombocytopenia

- Treatment: **Oprelvekin (Neumega, IL-11); Romiplostim** and **eltrombopag** (approved for idiopathic thrombocytopenia may also benefit).

Cancer Chemotherapy induced Nausea and Vomiting

- **Etiology:** Stimulation of CNS receptors, 5-hydroxytryptamine subtype 3 (5HT3) and neurokinin subtype 1 (NK1).
- **Highly emetogenic chemotherapy** drugs include **cisplatin**, carmustine, cyclophosphamide (>1.5 g/m²), dacarbazine, mechlorethamine, and streptozotocin.
- Treatment:
 - **5HT3-receptor antagonists:** Ondansetron, granisetron, dolasetron, tropisetron, and palonosetron.
 - **NK1 receptor antagonist:** Aprepitant.

Cancer Chemotherapy-induced GI Toxicity

- **Drugs MC a/w causing mucositis** in the mouth and the GIT are **cytarabine, 5-FU, and methotrexate**.
- Prevention of oral mucositis include the recombinant **keratinocyte growth factor inhibitor palifermin**
- **Diarrhea** is most a/w **fluorouracil, capecitabine, and irinotecan** as well as the **tyrosine kinase inhibitors** (sorafenib, sunitinib, imatinib, dasatinib) and **epithelial growth factor inhibitors** (cetuximab, panitumumab, and erlotinib).

Cancer Chemotherapy-induced Skin Toxicity

- **Hyperpigmentation** (liposomal doxorubicin, Imulfan, hydroxyurea)
- **Acral erythema (hand-foot syndrome)** and MC a/w administration of **fluorouracil, capecitabine, and liposomal doxorubicin**.

Hand-Foot Syndrome

- **Hand-foot syndrome** (acral erythema, palmar-plantar erythrodysesthesia) presents with tingling and burning of palms and soles that progresses to severe pain, tenderness, edema and plaque formation; can spread to dorsum of hands and feet.
- Treat by cessation of offending agent; **Pyridoxine** provides symptomatic relief.
- **Extra Edge: Hand foot syndrome** also refers to painful infarcts of the digits and dactylitis - in sickle cell disease.
- **Drugs causing hand-foot syndrome are**

Common drugs	Rarer drugs
• Capecitabine (MC)	• Cisplatin
• Doxorubicin	• Cyclophosphamide
• Cytarabine	• Daunorubicin
• 5-Fluorouracil	• Docetaxel, Paclitaxel
• Sorafenib	• Etoposide
• Sunitinib	• Hydroxyurea
	• Mercaptopurine
	• Methotrexate
	• Mitotane
	• Suramin
	• Tegafur

NEW AND RARE DRUGS

Drug	MOA	Uses
Avelumab	Anti PD1 (Programmed Death ligand 1 Ab	Metastatic Merkel cell carcinoma
Abemaciclib	Cyclin dependent kinase 4 and 6 inhibitor	ER/PR positive advanced or metastatic breast cancer as monotherapy or along with fluvestrant
Acalabrutinib	Bruton's tyrosine kinase inhibitor	Mantle cell lymphoma in patients who have received a least prior one therapy
Amantadine	NMDA antagonism	Dyskinesia in PD
Brodalumab	Anti IL-17 A receptor Ab	Plaque psoriasis
Brigatinib	Multikinase inhibitor	Advanced ALK-positive metastatic non-small cell lung cancer
Betrixaban	Oral factor Xa inhibitor	Prophylaxis of venous thromboembolism
Blinatumomab	Bispecific T cell Engager (BiTE) technology helps to engage the body's endogenous T cells to target malignant cells. Blinatumomab connects to the CD19 surface antigen on cells of B-lineage origin and the CD3 on T cells, creating a link.	For the treatment of Philadelphia chromosome-negative relapsed/refractory B cell precursor ALL
Canakinumab	Anti-IL-1 antibody	cryopyrin-associated periodic syndrome (CAPS)
Crisaborole	PDE-4 inhibitor	Topical treatment of atopic dermatitis
Copanlisib	Inhibitor of PI3 kinase- alpha and PI3 kinase- delta	Relapsed follicular lymphoma in adults with at least prior two systemic therapies
Cysteamine bitartrate	Converts Cystine to cysteine and thus prevents buildup of cystine within lysosomes	Cystinosis
Dupilumab	Anti IL-4 receptor alpha antibody	Atopic dermatitis
Defibrotide sodium	unknown	hepatic veno-occlusive disease with renal or pulmonary dysfunction following HSCT
Deflazacort	Corticosteroid	Duchenne muscular dystrophy
Deutetrabenazine	VMAT 2 Inhibitor	Huntington's chorea
Delaflaxacin	Fluoroquinolone	Acute bacterial skin and skin structure infections (ABSSSI) caused by both gram positive and negative organisms
Dapagliflozin + Saxagliptin FDC	SGLT2 Inhibitor + DPP-4 Inhibitor	Type II DM
Dolutegravir + Rilpivirine	Integrase Inhibitor + NNRTI	HIV1
Enasidenib	Inhibitor of the Isocitrate dehydrogenase 2 (IDH2) enzyme that works by blocking several enzymes that promote cell growth	Relapsed or refractory acute myeloid leukemia with IDH2 mutation
Edaravone	Free radical scavenger	ALS
Emicizumab-kxwh	Bispecific anti factor IXa and factor X antibody	Prevention of bleeding in patients with hemophilia A
Ertugliflozin	SGLT-2 inhibitor	Type II diabetes mellitus As monotherapy or along with sitagliptin or metformin
Eteplirsen		For the treatment of Duchenne muscular dystrophy with mutated DMD gene amenable to exon 51 skipping.

Contd.

Drug	MOA	Uses
Etanercept	Anti IL-23 MAb	Plaque psoriasis
Etelaprevir and Pibrentasvir FDC	Hep C protease Inhibitor And Hep C NSSA inhibitor	Hepatitis C
Erglucerase, velaglucerase, taliglucerase alfa	Recombinant DNA analog of beta-glucocerebrosidase	Enzyme replacement therapy for Gaucher's disease type 1
Eltuzumab ozogamycin	Anti CD-22 MAb	Relapsed or refractory B- cell precursor acute lymphoblastic leukemia
Elexacaftor	CFTR agonist	Cystic fibrosis
Elosulfuron + Allopurinol FDC	Uricosuric + Xanthine oxidase inhibitor	Gout in case of allopurinol ineffectiveness
Elvitegravir	Inhibits cytomegalovirus DNA terminase required for viral DNA processing and packaging, which results in improper virion maturation	Prevention of CMV infection in allogeneic hematopoietic stem cell transplantation in CMV seropositive recipients
Enloraustatin	Multikinase inhibitor	<ul style="list-style-type: none"> AML: Along with TOC (Cytarabine + Daunorubicin) in FLT3 mutation positive cases. Aggressive systemic mastocytosis Systemic mastocytosis with hematological neoplasm Mast cell leukemia)
Meropenem + Vaborbactam FDC	Carbapenem + Beta lactamase inhibitor	Complicated UTI
Heratnib	Inhibitor of EGFR, HER- 2 and Her-4 tyrosine kinase	Trastuzumab resistant breast cancer
Hexeritide	Human B-type natriuretic peptide (hBNP)	Acutely decompensated congestive heart failure
Netarsudil eye drops	Rho Kinase inhibitor lowers IOP by increasing aqueous humor outflow through trabecular meshwork	Glaucoma
Niraparib	Poly ADP-Ribose Polymerase (PARP) Inhibitor	Ovarian, fallopian tube and primary peritoneal cancer resistant to cisplatin
Naldemedine	Opioid antagonist	Opioid induced constipation
Netarsudil	Rho kinase Inhibitor which increases aqueous outflow through trabecular meshwork	Open angle glaucoma
Obiltoximab	Anti anthrax antibody	Anthrax
Ocrelizumab	Anti CD20 Ab	Multiple sclerosis: RRMS and PPMS
Olaratumab	Anti PDGFR-alpha antibody	Soft tissue sarcoma
Ozenoxacin	Topical fluoroquinolone	Impetigo caused by staphylococcus aureus and streptococcus pyogenes
Pimavanserin	Inverse agonist of 5-HT2A receptor	For the treatment of hallucinations and delusions associated with Parkinson's disease,
Pomalidomide	Thalidomide analog - Anti-angiogenic and inhibits myeloma cell growth	Multiple myeloma
Plecanatide	Guanylate cyclase c stimulator which acts by increasing cys GMP, which stimulates CFTR (Cystic Fibrosis Transmembrane Regulator), which increases Cl ion secretion into gut	Chronic Idiopathic constipation
Ramelteon	Melatonin agonist; selectively binds to the MT1 and MT2 receptors in the suprachiasmatic nucleus	Adults with Insomnia

Contd...

Contd...

Drug	MOA	Uses
Rivociclib	CDK (Cyclin Dependent Kinase) 4 and 6 inhibitor	ER +ve post menopausal breast cancer along with aromatase inhibitors
Rucaparib	Poly ADP Ribose Polymerase (PARP) inhibitor	Resistant ovarian cancer with BRCA mutation
Telotristat	Tryptophan hydroxylase inhibitor which inhibits serotonin synthesis	Carcinoid syndrome
Valbenazine	VMAT 2 Inhibitor	Tardive dyskinesia
Venetoclax	Anti-apoptotic protein Bcl-2 Inhibitor	CLL with 17p deletion
Vismodegib	Hedgehog pathway inhibitor	Metastatic basal cell carcinoma
Voretigene neparvovec		For the treatment of vision loss due to confirmed biallelic RPE65-mediated inherited retinal disease
Tavaborole	Inhibits fungal rprotein synthesis by inhibiting leucyl t-RNA synthetase	Onychomycosis
Ivermectin Cream		Rosacea
Pasireotide	Octerotide analog	Acromegaly
Suvorexant	Orexin receptor antagonist	For insomnia
Metreleptin	synthetic analog of leptin	Lipodystrophy
Eliglustat	inhibition of glucosylceramide synthetase	Gaucher's disease type 1
Vedolizumab	integrin blocker in the intestine	Ulcerative colitis and Crohn's disease
Umeclidinium inhalation powder	Long acting muscarinic antagonist	COPD
Ferric citrate		Hyperphosphatemia
Olaparib	PARP inhibitor (PolyADP Ribose Polymerase)	BRCA mutated advanced ovarian cancer
Pirfenidone	Antifibrotic by Inhibiting growth factors	Idiopathic pulmonary fibrosis
Isavuconazonium sulfate	Triazole antifungal agent	For the treatment of invasive aspergillosis and invasive mucormycosis
Panobinostat	Non-selective HDAC inhibitor (Histone Deacetylase)	For multiple myeloma
Palbociclib	CDK4 and CDK6 inhibitor	For the treatment of ER-positive, HER2-negative breast cancer,
Lenvatinib	Mutli kinase inhibitor	Thyroid cancers
Dinutuximab	Anti glycolipid GD2 antibody	high-risk neuroblastoma
Eluxadoline and Rifaximin		Irritable bowel syndrome with diarrhea,
Patiromer	Acts by binding free potassium ions in the gastrointestinal tract and releasing calcium ions for exchange,	treatment of hyperkalemia
Lesinurad	Urate transport URAT1 Inhibitor	treatment of hyperuricemia associated with gxxx
Cariprazine	D3 receptor agonist	schizophrenia and bipolar disorder
Trabectedin	Blocks DNA binding of the oncogenic transcription factor FUS CHOP	liposarcoma or leiomyosarcoma,
Asfotase alfa	Recombinant glycoprotein of Tissue nonspecific alkaline phsophatase	hypophosphatasia
Elbasvir	Hepatitis C NSSA inhibitor	HCV
Grazoprevir	Hepatitis C protease inhibitor	HCV

Contd

Contd

Drug	MOA	Uses
Secnidazole	Nitroimidazole	Bacterial vaginosis
Sarllumab	Anti IL-6 Mab	Rheumatoid arthritis
Tafinamide	MAO B inhibitor	On off phenomena seen with levodopa
Liraglutide	GLP1 agonist	Type II diabetes mellitus
Tafuprost	Prostaglandin analog, increases uveoscleral outflow	For reducing IOP In Glaucoma
Teixobactin	Inhibits cell wall synthesis by binding to Lipid II (peptidoglycan precursor). Being developed as "super-antibiotic" due to less chances of resistance.	Gram positive bacterial infections

Pathology

MCQ POINTS IN CELL BASICS

- The sequencing of the entire human genome—the Human genome project was completed in **2003**.
- The human genome contains approximately **3.2 billion** DNA base pairs.
- Within the genome there are about **20,000** protein-encoding genes constituting only about **1.5%** of the genome (implying that 98.5% of human genome does NOT encode proteins).
- ENCODE** = ENCyclopedia of DNA Elements started in 2007 to identify all regions of the human genome that could be ascribed some **function**.
- The **two MC forms of DNA variation** in the human genome are single nucleotide polymorphisms (**SNP**) and copy number variations (**CNV**).
- Nucleosomes** consist of DNA segments **147** base pairs long that are wrapped around a central core structure of highly conserved molecular weight proteins called **histones**.
- Examples of non-coding RNAs are—micro RNA (**miRNA**) and Long Noncoding RNA (**lncRNA**).
- Post-translational silencing of gene expression by miRNA** is a basic and well-conserved mechanism of gene regulation present in all eukaryotes (animals and plants).
- Cytoplasm** (cytosol) accounts for **maximum volume** of the cell (54%) and **second highest** volume is by **mitochondria** (22%, 1700 mitochondria/cell).
- Regardless of the nature of an extracellular stimulus (paracrine, synaptic or endocrine), the signal it conveys is transmitted to the cell via a specific **receptor protein**.
- Cell cycle progression is driven by proteins called “cyclins” and cyclin associated enzymes called “cyclin dependent kinases” (CDKs).
- Enforcing the cell cycle checkpoints is the job of CDK inhibitors (CDKIs).
- One family that **inhibits multiple CDKs** is composed of 3 proteins: **p21** (CDKN1A); **p27** (CDKN1B) and **p57** (CDKN1C).

- In the adult organism, stem cells replace damaged cells and maintain tissue populations as individual cells undergo **replicative senescence** due to **attrition of telomeres**.



Fig. 10.1: 'Rudolf Virchow', the father of cellular pathology

CELLULAR ADAPTATION

Hypertrophy

- Increase in **size of cells (cell mass)** but number remains the same.
- Due to increased production of cellular proteins.
- Physiological** hypertrophy: “**Pregnant uterus**” is mainly hypertrophy and some amount of hyperplasia.
- Pathological** hypertrophy: **Graves' disease**. **Smooth muscle** hypertrophy in **pyloric stenosis** or **left ventricular hypertrophy** in **systemic HTN**.

Hyperplasia

- Increase in **number of cells**, size remains the same.

Atrophy

- Both **number and size of cells are decreased**.

- Due to **decreased protein synthesis** and increased **protein degradation by ubiquitin-proteasome pathway**.
- Also due to increased autophagy.

Metaplasia

- Discussed under Oncology chapter (Pg 931).

CELL INJURY

- Adaptation**: Is the cell's response to prolonged stress.
- Cell injury**: Reversible (**hydropic change**) or irreversible (**necrosis and apoptosis**).
- Cell death**: **necrosis** (due to irreversible injury) and **apoptosis** (programmed cell death).
- General Mechanisms of Cell Injury:
 - ▶ **ATP depletion** - most critical mechanism
 - ▶ Oxygen derived **free radicals**.
 - ▶ Increased **intracellular calcium**
 - ▶ Defects in **membrane permeability**
 - ▶ **Mitochondrial dysfunction** - mitochondria is the first organelle to be affected.

Changes seen in reversible cell injury

- Cellular swelling - **earliest** change in all forms of cell injury (except **apoptosis** where **cell shrinkage** is earliest change!)
- Cytoplasmic vacuoles due to intracellular water accumulation - **hydropic** or **cloudy** swelling
- Plasma membrane alterations - **Bleb formation** and loss of microvilli
- Mitochondrial swelling** and **small amorphous densities** in mitochondria
- Endoplasmic reticulum swelling and degranulation of Rough ER
- Myelin figures** derived from damage of cell membrane

Changes seen only in irreversible cell injury

- Inability to reverse mitochondrial dysfunction
- Cell membrane rupture
- Lysosomal rupture
- Nuclear changes** - **pyknosis** (nuclear condensation), **karyorrhexis** (nuclear fragmentation) and **karyolysis** (loss of nuclear chromatin).
- Large flocculent densities** in mitochondria
- Myelin figures more prominent in irreversible injury
- Ca²⁺ influx** activates **phospholipase**, **protease** and **endonuclease**.

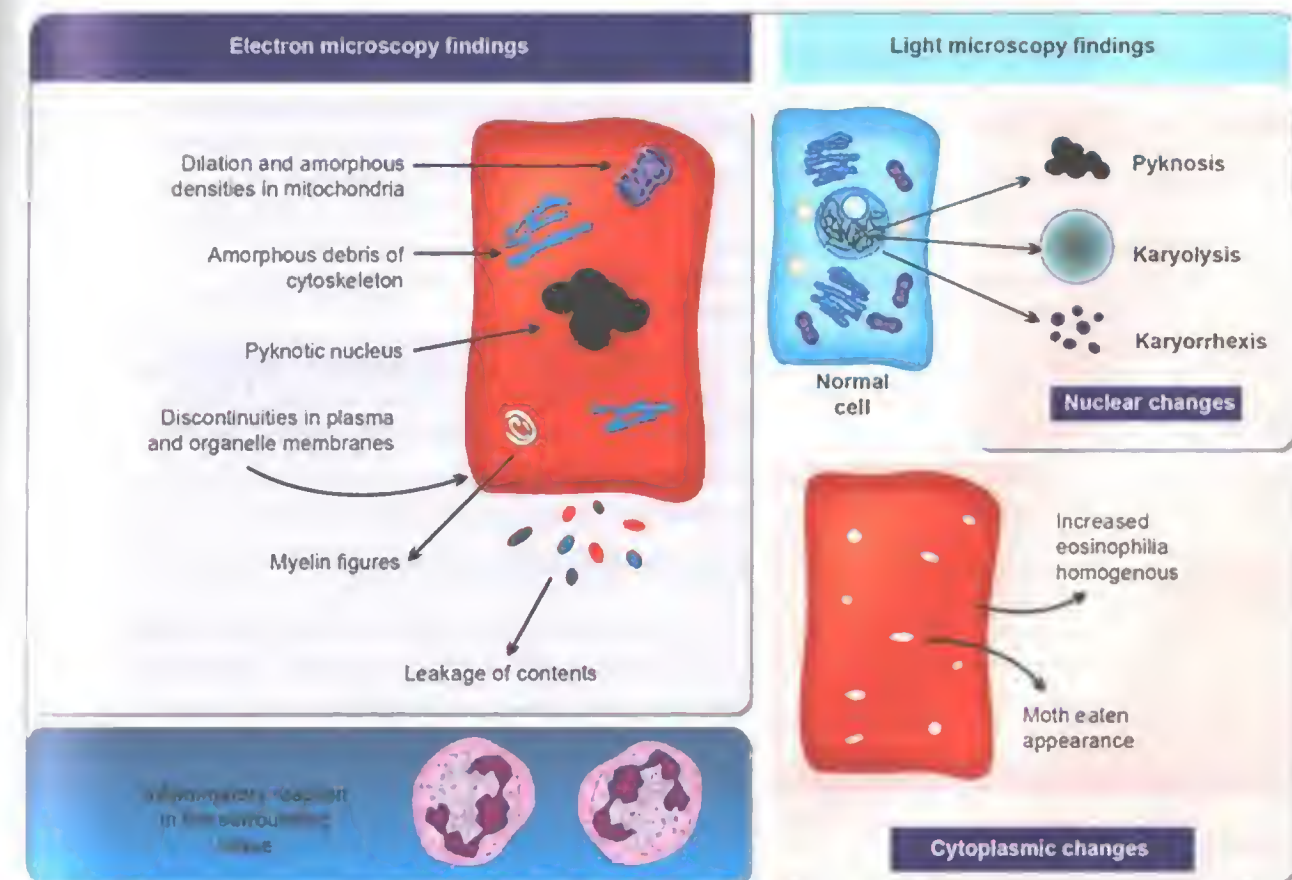


Fig. 10.2: Morphological changes in necrosis

Ischemia-Reperfusion Injury

- Ischemia-Reperfusion Injuries are damage due to restoration of blood flow to ischemic tissues (Contraction band in myocytes).
- It involves either *necrosis* or *apoptosis*.
- Seen in *myocardial infarction*, *stroke* or *acute renal failure*.

- Characteristically a/w *neutrophilic infiltrates*.

EXTRA EDGE

- **Neurons are most susceptible** to ischemia (irreversible damage within 3-4 minutes) > *myocardial cells* (irreversible damage in 20-30 minutes) > *fibroblasts* (most resistant to ischemic damage).

NECROSIS

Type of Necrosis	Features
Coagulation necrosis	<ul style="list-style-type: none">• MC type of necrosis• Typically caused by ischemia (infarct)• Cell appears <i>opaque, acidophilic</i> and retains its normal shape/architecture (NO enzymatic lysis occurs, only denaturation of proteins occurs) i.e. cells are converted into a microscopic "tombstone" – normal outline of the cell is retained but <i>cytoplasmic and nuclear details are lost</i>.• Occurs in:<ul style="list-style-type: none">- Myocardium (MC affected organ) by coagulative necrosis- Kidney, liver, spleen and other organs (NOT brain)- Mild burns (thermal injury)- Zenker's degeneration necrosis
Liquefaction (Colliquative) necrosis	<ul style="list-style-type: none">• Tissue is softened/liquefied due to enzyme action (autolysis and heterolysis)• Tissue architecture is lost• Seen in abscesses, brain infarction
Caseous necrosis	<ul style="list-style-type: none">• Induced by cell mediated immunity (T lymphocytes, macrophages, cytokines)• Tissue appears cheesy; histologically consists of granular material surrounded by epithelioid cells and multinucleated giant cells• Seen in tuberculosis, fungal granulomas (histoplasmosis and coccidioidomycosis)• Consists of both coagulative and liquefactive necrosis
Fat necrosis	<ul style="list-style-type: none">• Necrosis in adipose tissue induced by lipases (derived from injured pancreatic cells in acute pancreatitis) or trauma to adipose tissue (breast trauma)• Free fatty acids bind with calcium to form calcium soaps - Chalky white areas (fat saponification)
Fibrinoid necrosis	<ul style="list-style-type: none">• Typically seen in arteries, arterioles or glomerular capillaries damaged by autoimmune diseases• Blood vessels are impregnated by fibrin and other serum proteins and appear magenta-red on histology
Gangrenous necrosis	<ul style="list-style-type: none">• A clinical term for ischemic necrosis accompanied by bacterial infection which leads to partial liquefaction of tissues• 'Dry gangrene' (mummification) refers to noninfected ischemic necrosis accompanied by drying of the tissues• Wet gangrene: Toxins and enzymes released by superimposed bacterial infection converts dry to liquefactive pattern of wet gangrene.

APOPTOSIS

Definition

- A process of **cells undergoing programmed cell death**, whereby unwanted cells are removed by the activation of specific genetic pathways.

Functions of Apoptosis

- Elimination of cells in embryological development (e.g. motor neurones).
- Induction of tolerance to self-antigens by removal of autoreactive T lymphocytes.
- Removal of virally infected cells.

removal of cells, which have undergone DNA damage.

Morphologic features of apoptosis

- Earliest change: Cell **shrinkage**
- **Chromatin condensation** — Most characteristic feature
 - **Pyknosis**
- Formation of **cytoplasmic blebs** and **apoptotic bodies**
- Phagocytosis of apoptotic bodies by adjacent healthy cells and macrophages
- **Lack of inflammation**
- Because apoptosis occurs in single or small clusters of cells and **does not cause inflammation**, it may be difficult to demonstrate histologically.

Mechanisms of Apoptosis

- **Initiation**: consist of two pathways:
 - ▶ Intrinsic pathway: caspase 9 activation
 - ▶ Extrinsic pathway: caspase 8 activation.
- **Execution**:
 - ▶ Activation of **caspase-3** (most important), caspase 6 and 7
 - ▶ Initiator caspases activate executioner caspases which will be activating endonuclease and **chromatin clumping** occurs.
- **Mitochondria** plays a central role—**Increased mitochondrial outer-membrane permeability** is the major trigger of the **Intrinsic apoptosis pathway**
- Release of cytosolic **cytochrome C** from **mitochondria to the cytosol** is a **critical step in apoptotic cell death**
- **Annexin V** is marker of apoptosis.

Principal Mediators of Apoptosis

Positive regulators (proapoptotic)	Negative regulator (anti-apoptotic)
<ul style="list-style-type: none">• p53• Fas (CD95)• Caspases (initiators and executors of apoptosis)• BAX ; BAK• BAD, BID, PUMA	<ul style="list-style-type: none">• Bcl-2;• Bcl-XL• Mcl-1 (MC antiapoptotic gene a/w drug resistance to chemotherapy)• If it is overexpressed in tumours, cells have a prolonged survival

Detection of Apoptosis (Assays)

- Terminal deoxynucleotidyl transferase biotin - dUTP Nick End Labeling (**TUNEL**) technique for in vivo apoptosis detection.
- **DNA fragmentation assay**-observed by electrophoresis of genomic DNA; **apoptosis** will generate a "**step ladder**" in contrast to **necrosis** that will generate a continuous smear.
- **Annexin V/Propidium iodide** assay by flow cytometry or fluorescent microscopy.
- **Caspase activity** assay.

Examples of Apoptosis

Apoptosis for Proper Development of Tissues

- During formation of the fingers and toes of the fetus, the apoptosis plays an important role of **removing the web tissue between the finger and toes** - during **embryogenesis** (programmed destruction of cells).
- During sexual development in fetal life, apoptosis responsible for **regression of duct systems**.

Apoptosis for Normal Functioning of Adult Tissues

- **Endometrium** (Cyclic breakdown) and **prostate - hormone dependent involution** of tissues.
- **Epithelial cells** that lose their connection to the basal lamina and surrounding cells undergo apoptosis.
- Cell deletion in multiplying cell populations (**intestinal crypt epithelium**), **tumours** and **lymphoid organs**.

Apoptosis that Destroys Cells that Pose a Threat to the Integrity of the Organism

- Apoptosis of virus infected cells, cancer cells, cells with DNA damage, autoreactive immunocytes.
- Cell death by cytotoxic T cells, cell injury in certain viral diseases, atrophy in organs after duct obstruction.

Diseases of excess apoptosis	Diseases of insufficient apoptosis
Neurodegeneration HIV disease Myocardial infarction and stroke (ischemic injury) (CD4+ cells die through programmed cell death)	Cancer, Autoimmunity

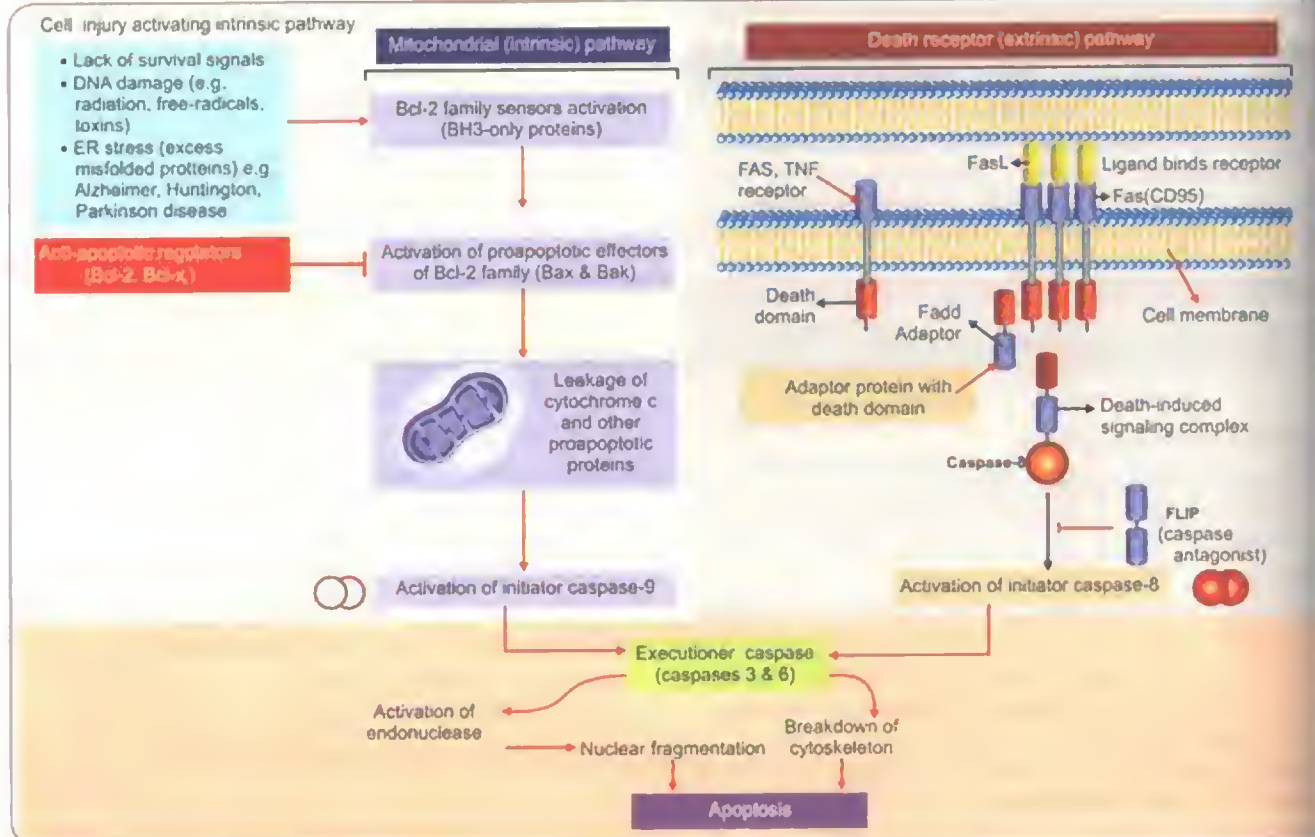


Fig. 10.3: Mechanism of apoptosis

EXTRA EDGE

- **Anoikis** is apoptosis caused by loss of cell to cell adhesion.
- **Diseases caused by misfolding of proteins**
 - Cystic Fibrosis
 - Familial hypercholesterolemia
 - Tay Sach's disease
 - Alpha-1-antitrypsin deficiency
 - Creutzfeldt Jacob disease
 - Alzheimer's disease

NECROPTOSIS

- A hybrid of necrosis + apoptosis BUT considered a part of necrosis.
- It is programmed cell death without caspase activation (caspase independent!).
- Maybe pathological (ischemic brain injury, viral infections) or physiological (mammalian bone growth plate).
- **Unlike apoptosis**, necroptosis shows cell swelling, cell membrane damage, increased lysosomal permeability and **inflammation is present**.

PYROPTOSIS

- A type of programmed cell death a/w **antimicrobial responses** during inflammation (innate immunity response).
- Requires **caspase 1 and 11**.
- Initiation of pyroptosis is caused by **recognition of flagellin components of Salmonella and Shigella species by NOD-like receptors**.

AUTOPHAGY

- A process in which **cell eats its own contents**. In the process cytoplasmic materials are transported to lysosome for degradation.
- **Macroautophagy: Major form** of autophagy; involves **autophagosome** formation.
- **Microautophagy:** lysosomal membrane's inward invagination for transport.
- **Chaperone mediated:** direct transport through lysosomal membrane by chaperones.
- 2016 Nobel prize in physiology/medicine was awarded to Yoshinori Ohsumi—for the work on autophagy.

PATHOLOGIC CALCIFICATIONS**Dystrophic calcification**

Occurs in nonviable or dying tissues in the presence of **NORMAL** serum calcium levels

Seen in

- **Caseous** necrosis (TB).
- Liquefactive necrosis (abscess).
- Fat necrosis, Atherosclerosis,
- Damaged/rheumatic heart valves,
- Stroma of some tumours
- **Psammoma** bodies

Metastatic calcification

Occurs in normal tissues and results from **hypercalcemia**. **MC cause is primary hyperparathyroidism** (All conditions which cause hypercalcemia may cause metastatic calcification)

Seen in

- Alveolar wall of lung (**MC site**)
- Basement membrane and tubular lamina of **kidneys, lungs**
- Interstitial tissues of **gastric mucosa**
- Systemic arteries and pulmonary veins
- Cornea and conjunctiva
- Synovium of joints
- Tendons

EXTRA EDGE

- In dystrophic calcification, intracellular **calcification begins in mitochondria** of dead or decaying cells.
- **Stains used for Calcium:** von Kossa, Alizarin red; Calcein stain, Tetracycline labeling index.

INTRACELLULAR ACCUMULATIONS**Lipids**

- Intracellular lipid accumulation is called **fatty change or steatosis** - **MC site is liver**.
- **MC form** of lipid accumulated is **triglycerides**; others include cholesterol esters and phospholipids.
- **Special stains used for lipids/fats are:**
 - ▶ **Oil red O** stain
 - ▶ **Sudan Black or Sudan IV**
 - ▶ **Osmium tetroxide**.
- **Tigered/tigroid/tabby cat myocardium** - also called **thrush breast heart** - due to alternate bands of dark and normal myocardium with yellow abnormal lipid accumulations. - seen in **prolonged moderate hypoxia**.

Cytoskeletal Proteins

- **Intermediate filaments** provide flexible scaffolding for structural support of cells. Excess intermediate filaments are hallmark of cell injury.

Types of intermediate filaments	Cell in which seen
Keratin filaments	Epithelial cells; also form Malory Denk bodies in alcoholic liver disease
Neurofilaments	Neurons; responsible for neurofibrillary tangles of Alzheimer's disease
Desmin filaments	Muscle cells
Vimentin filaments	Connective tissue cells
Giant fibrillary acidic proteins (GFAP)	Glial cells.

Pigments

- **Lipofuscin:**
 - ▶ A.k.a **lipochrome, wear and tear pigment, aging pigment**.
 - ▶ It is a **perinuclear brown pigment** and its presence is a sign of **free radical injury (brown atrophy)**.
 - ▶ It is seen in **aging, cancer cachexia and severe malnutrition**.
 - ▶ **Carcinoid gross specimen** is dark brown due to presence of lipofuscin.
- **Melanin:** Endogenous black pigment detected by **Fontana** stain.
- **Homogentisic acid:** a.k.a **ochronosis** in **alkaptonuria**; due to **lack of homogentisic acid oxidase**.
- **Hemosiderin:** Hemoglobin derived golden brown pigment composed of aggregated ferritin micelles; detected by **Perl's Prussian Blue** staining.

Free radical induced cell injury

- ▶ Cell injury induced by free radicals is an important mechanism of damage in some conditions — **chemical and radiation injury, ischemia reperfusion injury** and in **cellular aging**.
- ▶ **Reactive oxygen species (ROS)** are a type of oxygen derived free radical whose role in cell injury is well-established. They include:
 - O_2^- (Superoxide anion)
 - H_2O_2 (Hydrogen peroxide)
 - OH (Hydroxy radical)
 - $ONOO$ (peroxynitrite)
- ▶ **Enzymes** involved in inactivation of free radicals are
 - Catalase (present in peroxisomes decomposes H_2O_2)
 - Superoxide dismutase (converts O_2^- to H_2O_2)
 - Glutathione peroxidase
- ▶ The **Fenton reaction** (shown below) results in the creation of hydroxyl radicals from hydrogen peroxide and an iron catalyst. Iron is regenerated via the **Haber-Weiss reaction**.
 - ▶ $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$

CELLULAR AGING: HIGH YIELD POINTS

- Changes seen during aging are:
 - **Increased free radicals** and decreased antioxidants (Most widely accepted theory for aging)
 - Increased collagen **cross linking**
 - **Decreased** expression of **IGF-1** gene (Insulin Like Growth Factor-1)
 - **Telomere shortening**.
- Normal human cells are capable of 60-70 times of cell division in one lifetime; this is due to progressive telomere shortening with each division - called as **Hayflick limit** or **Hayflick phenomenon**.
- **Wermer's syndrome: premature aging** due to defective **DNA helicase** (NOT the same Wermer syndrome, as MEN-1).

	G1	S	G2	M	G0
Synonym	Presynthetic phase (Gap1 or interphase)	Synthetic	Postsynthetic	Mitotic	Quiescent/ resting phase
Features	Most variable phase; Maximum part of cell cycle (40%)	Chromosomal	Cell cycle arrest due to p53	Rate of protein and RNA syntheses ↓ abruptly	Gene transcription
Events	Cell growth (cellular content of DNA doubles) RNA synthesis Protein synthesis	DNA synthesis	RNA synthesis Preparation for mitosis ATP synthesis	Shortest part of cell cycle (2%)	
Importance	Growth factors are most effective First checkpoint in cancer cells	In malignant cells there is ↑ in nuclear: cytoplasmic ratio	G2-M is the most sensitive phase of the cell-cycle to radiation		Nonproliferating cells remain in G0 phase
Blocked by	Vinblastine	MTX, Doxo, cytarabine, 6-TG, hydroxyurea, mitomycin C, 6-MP	Bleomycin, Topotecan, etoposide, daunorubicin	Vincristine/blastline (break microtubules), paclitaxel (stabilizes), colchicine	

- **Checkpoints** verify whether the processes at each phase of the cell cycle have been accurately completed before progression into the next phase
- Two main checkpoints are G1→S checkpoints (restriction) and G2→M checkpoint
- **p53** is a tumor suppressor gene that normally inhibits G1→S progression; mutations in this gene results in unrestrained cell growth -hence p53 is called

- Most effective way to prolong lifespan is **caloric restriction**; caloric restriction will induce **sirtuins** (which can be induced by **red wine**).
- **Role of Sirtuins**: Inhibit metabolic activity reduce apoptosis; stimulate protein folding; inhibits free radical damage; increase insulin sensitivity and glucose metabolism.

CELL CYCLE

G1 → S → G2 → M → G1 → G0

- If there is a **block prior to G2 phase** by TGF-beta, there will be **increase in cell size (cell hypertrophy)**.
- If there is a **block after M**, cells do not enter quiescent phase and it leads to **increase in cell numbers (cell hyperplasia)**.

"guardian of G1 checkpoint/guardian of genome molecular policeman"
➤ The **G2/M DNA checkpoint** is regulated by **Cyclin B-cdc2 (CDK1) complex**.

EXTRA EDGE

- **RB gene**: Governor of **proliferation**
- **p53**: **Guardian of genome**
- **APC**: **Gatekeeper of colonic neoplasia**.

Types of Cells

Cell	Description
Labile cells (Continuously dividing, inter-mitotic cells)	(Never go to G0, divide rapidly with short G1) Surface epithelial cells (of epidermis, GIT, respiratory tract, urinary tract, vagina, cervix, endometrium) Hair follicles Haematopoietic/bone marrow cells
Stable cells (Quiescent)	(Enter G1 from G0 when stimulated) Normally with slow turnover but capable of rapid division in response to stimuli — parenchymal cells (of liver, pancreas, kidney, thyroid, adrenals); mesenchymal cells (smooth muscle cells, fibroblasts, endothelial cells)
Nondividing (Permanent)	(Remain in G0, regenerate from stem cells) Cells which CANNOT undergo division in postnatal life . Eg, neurons, skeletal muscle, cardiac muscle .

STEM CELLS

Stem Cells are Cells which have Two Unique Properties

- **Self renewal** by:
 - **Asymmetric replication**: means that, in every cell division, one of the cells retains its self renewing capacity while the other cell enters a differentiating

pathway and gets converted to mature non-dividing population.

- **Symmetric replication**: produces two identical daughter cells.
- **Potency**- refers to ability of stem cells to differentiate into specialised (mature) cell types.

Types of Stem Cells based on Potency

- **Totipotent** stem cells:
 - Produced from **fertilisation of the ovum**
 - They can differentiate into **all types** of embryonic or extraembryonic cell.
- **Pluripotent** stem cells:
 - Derived from **totipotent stem cells**
 - They can differentiate into cells derived from **any of three germ layers**.
- **Multipotent** stem cells:
 - They can only differentiate into closely related family of cells
 - Ex: Hematopoietic stem cells can only differentiate into RBC, WBC and platelets; they cannot form other types of cells.
- **Unipotent** stem cells:
 - They can differentiate into **only one cell type**
 - Ex: muscle stem cells will form muscle stem cells only.

Adult (Somatic) Stem Cells

After their formation in the fetus, some tissues and organs continue to maintain a population of stem cells through childhood into adulthood.

Stem cell	Location	Comments
Liver stem cells	At canals of Hering (junction between hepatocytes and biliary system)	They form bipotent progenitor called oval cells ; they can form hepatocytes or biliary epithelium
Skin stem cells	At hair follicle bulge, epidermal interfollicular region and sebaceous glands	A.k.a bulge stem cells ; they can replenish epithelium after wounding
Corneal stem cells	Located between epithelium of cornea and conjunctiva	A.k.a limbal stem cells
Small Intestinal crypt epithelial stem cells	Immediately above Paneth cells	
Skeletal muscle stem cells	Located at basal lamina of myotubes	A.k.a satellite cells ; it helps in regeneration of injured skeletal muscle
Brain	At dentate gyrus of the hippocampus and subventricular zone;	A.k.a Neural stem cells ; Capable of generating neurons, astrocytes and oligodendroglial cells
Umbilical cord blood and placental stem cells	Derived from umbilical cord blood	Banked (cryopreserved) for future use, if necessary
Dental stem cells	In pulp of teeth	

EXTRA EDGE

- **Bone Marrow stem cells** - contains 2 types of stem cells:
 - **Pluripotent stem cells**: capable of regenerating all blood cell elements.
 - **Marrow stem cells** are multipotent and capable of differentiating into bone, cartilage, fat, muscle, endothelium, depending on the tissue into which they migrate.

ACUTE INFLAMMATION

Classical Signs of Acute Inflammation

- 4 classical signs described by Celsus:
 - **Rubor** (redness)
 - **Tumor** (swelling)
 - **Dolor** (Pain)
 - **Color** (heat)
- **Functio Laesa** (loss of function) - fifth clinical sign later added by Virchow.

Vascular Events of Acute Inflammation

- **Vasoconstriction**:
 - **Earliest and transient** change - responsible for blanching seen immediately after injury.
- **Vasodilation**:
 - It **first involves arterioles** and **increases hydrostatic pressure**; responsible for **redness (dolor)** and **warmth**.
- **Increased vascular permeability**:
 - **Hallmark** of acute inflammation
 - Affects **venules** mostly
 - **MC mechanism** is **endothelial gap** formation - occurs due to **contraction of endothelial cytoskeleton**.
- **Stasis**:
 - Increased vascular dilation and fluid loss will increase viscosity and RBC concentration and develop stasis.

Cellular Events of Acute Inflammation

- **Margination**:
 - Leucocytes at the periphery of blood vessels transiently adhere to the endothelium with help of selectin molecules (CD 62).
- **Rolling**:
 - Leukocyte movement with intermittent attachment and detachment of receptors with endothelium - due to **selectin** molecules (mainly **P and L selectins**).
- **Adhesion**:
 - Firm adhesion of leucocytes to endothelial cells; mainly mediated by **Integrin**.

Adhesion molecules have 4 families

- **Selectin (CD 62)**
 - Function in **cell-cell interaction** only.
 - **E selectin** (present in **endothelium** and binds to Sialyl Lewis ligand on leukocytes)
 - **P selectin** (present on **platelets** and endothelium both and binds to Sialyl Lewis ligand on leukocytes)
 - **L selectin** (present on platelets and binds to mucin like glycoprotein GlyCAM-1 on endothelium).
- **Integrins**
 - Present on leucocytes for **both cell-cell and cell-matrix** interaction
 - **B1 Integrin** binds with **VCAM-1** (Vascular adhesion molecule)
 - **B2 Integrin** binds with **ICAM-1** (Intracellular adhesion molecule-1).
- **Mucin like glycoprotein**
 - They are present on cell surface and extracellular matrix (ex: **heparin sulphate**)
 - Leukocyte adhesion molecule **CD 44** binds to **heparin sulphate**.

- **Pavementing**:
 - Endothelial lining covered by leucocytes.
- **Diapedesis (Transmigration)**:
 - It is **transmigration of leucocytes through endothelial gap**.
 - It **occurs mostly in post capillary venules** except in **lungs** where it occurs in capillaries.
 - Cytokines activate leucocytes and endothelial cells to induce expression of adhesion molecules - **PECAM-1** (Platelet endothelial cell adhesion molecule, **CD 31**) is the **MOST important** adhesion molecule in **diapedesis**.
- **Chemotaxis**:
 - Unidirectional movement of leucocytes towards chemotactic stimuli. Chemotactic stimuli may be:
 - **Complements: C5a (most powerful) > C3a > C4a**
 - **Leukotriene B4** for **IL-8** (for neutrophils).
- **Phagocytosis**:
 - Phagocytosis is further described separately below

Morphological patterns of Acute Inflammation

- **Catarrhal inflammation**
 - Inflammation of mucus membranes causes **increased mucus secretion**; **MC type** of acute inflammation; **MC** occurs in nose, pharynx and ear after URTI.
- **Serous inflammation**
 - Outpouring of serous fluid from mesothelial cells lining peritoneal, pleural or pericardial cavities; **MC example** is **blister formation after burns**.
- **Fibrinous inflammation**
 - Fibrin is deposited in extracellular space due to increased vascular permeability. It is seen in cavities like **meninges, pericardium and pleura**.

PHAGOCYTOSIS

- **Elie Metchnikoff** discovered phagocytosis
- **Phagocytic cells** are **neutrophils, monocytes, macrophages** and **eosinophils** (for parasites).
- Phagocytosis consists of **engulfment, killing and degradation** of microbes. It consists of 3 essential steps.
- **Recognition and attachment**:
 - It starts with leucocyte receptors binding to the microbes. These receptors are:
 - Mannose receptors: They bind to mannose anducose of microbial cell wall; normal human cells are protected from phagocytosis due to presence of N-acetyl galactosamine or terminal sialic acid.
 - Scavenger receptors.
 - Opsonin receptors: Opsonins are molecules to bind microbes and enhance phagocytosis; Ex: IgG (best opsonin); C3b (best complement opsonin); Lectins.
- After the first step, i.e. opsonisation of microbes by complements and antibodies, there will be attachment between opsonin receptor (C3b or Fc fragment) to **scavenger receptor (Fc gamma 3R)** of phagocytic cells.
- **Engulfment**:
 - Engulfment begins with cytoplasmic **pseudopods** formation > these enclose the particle to form **phagosome** > fuse with lysosomes to form **phagolysosomes** > followed by **rupture of lysosomal granules**.

EXTRA EDGE

- Both **phagocytosis** and **chemotaxis** require **polymerisation of actin** filaments.
- **Pinocytosis** (cell drinking) and **endocytosis** require **clathrin** coated pits.
- Disorders of phagocytosis - **chronic granulomatous disease** and **Chediak Higashi syndrome** are discussed under Immunology chapter (Pg 314).

INFLAMMATORY MEDIATORS

Cellular mediators (present within cells)	Plasma mediators (synthesised by liver and secreted into plasma)
Preformed cellular mediators:	
• Histamine	• Coagulation and Kinin system
• Serotonin	• Complement system
• Lysosomal enzymes	
• Neuropeptides	

Contd...

Contd...

Cellular mediators (present within cells)	Plasma mediators (synthesised by liver and secreted into plasma)
--	--

Newly synthesised cellular mediators

- Nitric Oxide
- Cytokines
- Chemokines
- Platelet activating Factor
- Arachidonic acid metabolites

EXTRA EDGE

- **Arachidonic acid metabolites** are discussed under **Biochemistry** chapter (Pg 327).
- **Complement system** (discussed under **Immunology** chapter (Pg 309).

Histamine

- Synthesised from **histidine**; richest source is **mast cells**.
- Causes **vasodilation**; **increased vascular permeability** and **smooth muscle constriction** (bronchoconstriction).

Serotonin

- A.k.a **5-hydroxytryptamine**; richest source is **platelets** but maybe present in **enterochromaffin cells**.
- Functions are same as histamine above.

Lysosomal Enzymes

- They are present in lysosomes of neutrophils and monocytes.
- Three types of lysosomal granules are: **Primary (azurophilic)**, **secondary (specific)** and **tertiary granules (C-particles)**.

Primary (azurophilic) granules	Secondary (specific) granules	Tertiary granules (C-particles)
Develops at promyelocytic stage More destructive	Develops at myelocytic stage Less destructive	Mainly involved in chemotaxis, diapedesis and matrix degradation
It contains Myeloperoxidase (MPO); elastase; defensins; cathepsin G; acid hydrolase; phospholipase A-2; Bacterial permeability proteins	It contains Lactoferrin; lysozyme; type IV collagenase; b2 microglobulin; gelatinase; cytochrome B and vitamin B12 binding proteins	It contains gelatinase

Neuropeptides

- Examples are **substance P** and **neurokinin A**.
- Nerve fibres containing substance P is rich in **lung and GIT**.
- Secreted by sensory nerves and leucocytes.
- Actions are:
 - **Pain** signal transmission
 - **BP** regulation
 - Mediator of vascular permeability
 - Stimulates immune and endocrine cell secretion.

Nitric Oxide (NO)

- Most important physiological source of **NO** is **endothelial cells**. It is a primary determinant of **resting vascular tone**.
- Synthesised from **arginine** by **cytosolic nitric oxide synthetase (NOS)**.
- **3 isoforms** of Nitric oxide synthetase are:
 - **Neuronal NOS** (nNOS or NOS-1)
 - **Macrophage or Inducible NOS** (iNOS or NOS-2)
 - **Endothelial NOS** (eNOS or NOS-3)
- NOS-1 and NOS-3 are activated by calcium.
- NOS is a very complex enzyme requiring 5 cofactors - NADPH; FAD; FMN; heme and tetrahydrobiopterin.
- NO acts through cGMP as second messenger.
- Actions are:
 - **Relaxes smooth muscles** in blood vessels (causes vasodilation) and in GIT
 - **Vasodilation**: helps in penile erection (by vasodilation in corpora cavernosa)

- **Inhibits** platelet aggregation
- Microbicidal action (by forming **peroxynitrite** free radical).
- **Cigarette smoking decreases endogenous NO** formation.

Cytokines

- They are soluble polypeptides; secreted by **both** hematopoietic and nonhematopoietic cells; they are highly specific.

Important cytokines and their actions

- Fever - **IL-1**
- Angiogenesis - **VEGF**
- Fibrosis - TGF-beta
- Both morphogenic and mitogenic - BMP (Bone morphogenic Protein)
- Anti-inflammatory - IL-4, 6, 10, 13, TGF-β
- Both pro and anti inflammatory - IL-4 and IL-6
- Synthesis of acute phase proteins - IL-6
- Granuloma formation - IFN gamma
- TNF-alpha-Acute inflammation, septic shock, SIRS, and cachexia.

Chemokines

- These are a family of **small proteins** (8-10 kD) which **stimulate chemotaxis** (leucocyte movement).
- They are classified into **4 major groups** on the basis of arrangements of **Cysteine** residues as in table below.
- They perform their actions by binding to **7 G protein** couple receptors.

C-X-C (Alpha chemokines)	C-C (beta chemokines)	C (Gamma chemokines)	CX3C
Recruit neutrophils IL-8 is a typical member; others are IL-1 and TNF-alpha	Recruit monocytes, basophils and lymphocytes but NOT neutrophils Members are Eotaxin (for Eosinophils) Monocyte chemoattractant protein-1 RANTES MIP-1 alpha (Macrophage inflammatory protein)	Recruit lymphocytes only Member is lymphotactin	Only member is Fractalkine

Platelet Activating Factor

- **Most potent** inflammatory mediator (more potent than histamine).
- Causes:**
 - Platelet aggregation
 - Vasoconstriction and bronchoconstriction
 - **At low doses** it induces vasodilation and increased vascular permeability
 - **Transmits signals** between **neighbouring** cells.

Coagulation and Kinin System

- Inflammation promotes clotting by increasing production of several coagulation factors.
- Thrombin promotes inflammation by binding to **protease activated receptors (PARs)** on platelets, endothelium and smooth muscle cells.
- **Bradykinin:**
 - Activated factor XII (called XIIa) cleaves prekallikrein to active kallikrein; Kallikrein converts circulating HMW kininogen to bradykinin.

- It causes vasodilation, increased vascular permeability and pain.
- **Kallikrein:**
 - Potent activator of factor XII; has direct chemotactic activity and converts C5 to C5a.

Summary: Role of Mediators in Different Reactions of Inflammation

Reaction	Mediators
Vasodilation	Prostaglandins, NO, histamine
Increased vascular permeability	Histamine, C3a and C5a, Bradykinin, Leukotrienes C4, D4 and E4, PAF, Substance P
Chemotaxis, Leukocyte recruitment and activation	C5a (most potent chemoattractant), Leukotriene B4, Chemokines, IL-1 and TNF, Bacterial products
Pain	Substance P; Prostaglandins, Bradykinin
Tissue damage	NO, Neutrophil and macrophage lysosomal enzymes, O ₂ metabolites

CHRONIC INFLAMMATION

Chronic Inflammation is Characterized by:

- **Mononuclear inflammatory cell infiltration** (macrophage is most important)
- **Tissue destruction** (hallmark of chronic inflammation)
- **Wound healing** with fibrosis and angiogenesis.

Granulomatous Inflammation

- A distinctive form of chronic inflammation consisting of granuloma formation.
- Granuloma consist of 3 components:
 - **Epithelioid** cells (activated macrophage)
 - **Collar of lymphocytes** and occasional plasma cells
 - **Multinucleated giant cells** (formed by fusion of epithelioid cells).
- Granulomas maybe divided into:

Immunological granuloma	Nonimmune granuloma
<ul style="list-style-type: none"> • MC type; a.k.a hypersensitivity granuloma • It is lymphocyte mediated • Examples are: <ul style="list-style-type: none"> TB Leprosy Cat Scratch disease Sarcoidosis Blastomycosis Histoplasmosis Hodgkin's lymphoma. 	<ul style="list-style-type: none"> • NOT a/w lymphocytes • Formed by poorly digestible substances • Examples are: <ul style="list-style-type: none"> - Silicosis - Foreign body type pneumonia.

Caseous Necrosis in Granuloma

Caseating granuloma is seen in:

- TB
- Syphilis and
- Histoplasmosis
- Coccidioidomycosis.

Necrosis in Granulomas

Necrotic/Necrotising granulomas seen in

- TB
- Histoplasmosis
- Syphilis
- Coccidioidomycosis
- Cat scratch disease
- Blastomycosis
- Wegener's granulomatosis and
- Rheumatoid Arthritis (RA).

Must Know points about Granulomas

- **Interferon Gamma** is the **most important cytokine** for **granuloma formation** - induces conversion of activated macrophages into epithelioid cells.
- **TB** can have BOTH caseating and NON caseating granuloma.
- **Sarcoidosis** classically has NON caseating granuloma.
- Most important T cell in granuloma formation - **CD4 helper T cells** (Th1CD4).
- **Stellate granuloma** - granuloma with central neutrophilic infiltrate - seen in **Cat scratch disease** and LGV.
- **Durck's granuloma** - seen in **cerebral malaria** caused by **plasmodium falciparum**.
- **Eosinophilic granuloma** - see in **Churg Strauss** syndrome and parasitic infections.

Giant Cells

- Activated macrophages - transforms to epithelioid cells - these fuse to form **multinucleated giant cells**.
- **Langhan's type** Giant cell - nuclear arrangement is peripheral.
- **Foreign body type** giant cell: Haphazard arrangement of nuclei.
- Giant cells examples are in below table:

Cell	Comments
Aschaff Giant cells	Diagnosis of Rheumatic Fever
Warthin Finkeldey Giant cells	Measles
Taurot Giant cells	A lipid-laden histiocyte in which multiple nuclei are grouped around a small island of cytoplasm

Contd...

Contd...

Cell	Comments
	Seen in fat necrosis, xanthoma, xanthogranuloma and dermatofibroma
Reed Sternberg's cell	Hodgkin's lymphoma
Physiological Giant cells	Bone Marrow - Osteoclast and megakaryocytes Placenta - Syncytiotrophoblast

Acute Phase Reactants

- Acute Phase Reactants are a **class of proteins** whose concentration increases (by 25% of normal, positive) or decreases (by 25% of normal, negative) in response to inflammation.

Positive Acute Phase Reactants	Negative Acute Phase Reactants
CRP (C Reactive Protein) HSCRP (highly sensitive CRP) Fibrinogen Plasminogen activator inhibitor Serum amyloid A Ferritin Ceruloplasmin Haptoglobin Hepcidin	Albumin Prealbumin (Transthyretin) Transferrin IGF-1

WOUND HEALING

Wound Healing Consists of Three Processes

- Resolution:** Ideal outcome of healing seen in acute inflammatory response to minor injuries.
- Regeneration:** Protective mechanisms of epithelial cells where lost parenchymal cells are replaced by division of adjacent normal parenchymal cells. There will be complete restoration of normal tissue.
- Repair:** A process of replacement of damaged tissue by fibrocollagenous tissue. It consists of two events:
 - Granulation Tissue Formation:**
 - Hallmark of Wound healing** - occurs due to proliferation of new blood vessels (angiogenesis), budding of new capillaries and proliferation of fibroblasts.
 - Early granulation tissue** consists of **collagen types 1 and 3**. (scar tissue and adult skin will have type 1 collagen only).
 - Wound contraction and scar formation:**

- Myofibroblasts** are responsible for **wound contraction**.
- Replacement of granulation tissue with scar is called **remodeling**.
- Collagen degradation is important for tissue remodeling and is done by **matrix metalloproteinases (MMP)**.
- Zinc** is most important factor of activity of matrix metalloproteinase.

Cutaneous Wound Healing Changes

- Immediately:** **Fibrin and platelets** form clot
- Day 1:** **Neutrophils** and blood clots
- By 24-48 hour:** **epithelial closure** takes place
- On day 3:** neutrophils are replaced by **macrophages**; **granulation tissue appears**
- By day 5:** Collagen fibrils begin to appear and **epithelial proliferation is maximal**
- 2nd week:** Disappearance of edema and leukocytes; presence of **fibroblasts** (derived from local mesenchyme) and **maximum collagen**
- End of 1 month:** Scar with intact epidermis
- During repair,** the initial matrix is called "**provisional wound matrix**" that contains **platelets, fibrinogen, fibrin and fibronectin**.

Wound Strength

- Cross linking of collagen** is the most important factor for tensile strength of collagen.
- At the **end of first week:** wound strength is approximately 10%.
- By **3 months:** Recovery of **tensile strength is 70-80%** (this the **maximum strength**, 100% is **never regained!**).

Pathological Aspects of Repair

- Proud flesh:** Excessive **granulation tissue**; it blocks re-epithelialisation.
- Hypertrophic scar:** Excessive collagen accumulation forms a raised scar within wound boundaries; **spontaneous regression** occurs in 12-18 months.
- Keloid:** Scar progression **beyond** the original area of injury without subsequent regression; **MC** seen in **Africans**; **MC** site is **sternum**; NO spontaneous regression

MODYNAMICS

Hyperemia and Congestion

Hyperemia	Congestion
Active hyperemia refers to arteriolar dilatation of sympathetic or humoral origin, e.g. Usually a physiologic response to increased functional demand as after exercise or in inflammation.	Passive hyperemia (Congestion) results from impaired venous drainage and engorgement of organ with venous blood.

Chronic venous congestion of the liver	CVC of lungs
<ul style="list-style-type: none"> Seen in Right ventricular failure - leads to 'Nutmeg' liver. With severe CVC of liver, fibrous thickening of the walls of the veins and central sinusoids leads to 'cardiac sclerosis' ('cardiac cirrhosis'). 	<ul style="list-style-type: none"> Seen in left ventricular failure; if chronic leads to - edematous hemostiderin laden septa become fibrotic - 'brown induration of lungs' 'Heart failure cells' hemostiderin laden intra-alveolar macrophages.

Thrombosis

Formation of a clotted mass of blood (thrombus) within the uninterrupted vascular system. This is influenced by **Virchow's triad** which consists of:

- Endothelial injury** (most important), alone can induce thrombosis
- Normal blood flow disturbances** (stasis and turbulence of blood)
- Hypercoagulability**

Arterial thrombi	Venous thrombi
Thrombin are grey-red, nonocclusive (mural), with pale layers of platelets and fibrin alternating with darker layers containing more abundant RBCs (lines of Zahn - coralline thrombus).	Thrombi are red-blue, lines of Zahn only rarely evident.
Common in coronary, cerebral, iliac and femoral arteries .	Common in deep leg veins, femoral and iliac veins and rarely superficial varicose veins.

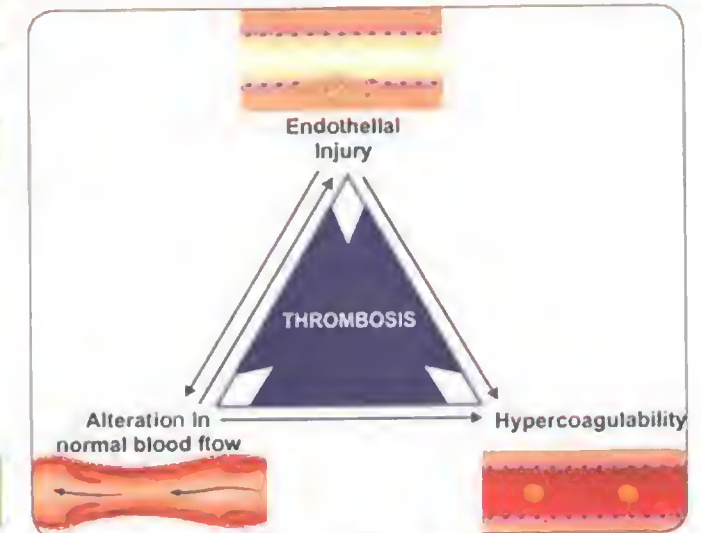


Fig. 10.4: Virchow's triad in thrombosis. (1) Endothelial injury is the most important factor, (2) Alteration in blood flow (stasis or turbulence) and (3) Hypercoagulability

Few Terms

- '**Currant-jelly**' clots: **Post-mortem clots** which are not attached to the vessel wall; helps to differentiate from ante-mortem thrombi.
- Trousseau's phenomenon:** (**migratory thrombophlebitis**) seen in **disseminated visceral cancers** (most often in **Ca pancreas and GIT cancers**, also lungs, prostate, female reproductive tract, breast).
- Phlegmasia alba dolens** (painful white leg): **iliofemoral venous thrombosis** due to **gravid uterus** compressing the inferior vena cava causing venous stasis in the legs.
- Phlegmasia cerulea dolens** (painful blue leg): swollen bluish skin with **superficial gangrene**, occurring as a complication of **iliofemoral venous thrombosis** and **decreased arterial blood flow**.

Types of Embolism

- Thromboembolism (MC):** embolism of thrombus or blood clot.
- Cholesterol embolism:** embolism of cholesterol, often from atherosclerotic plaque inside a vessel.
- Fat embolism:** embolism of fat droplets; intravascular fat globules in microvessels, especially in lungs, kidneys, brain. Requires special **fat stains (oil-red O)** and avoidance of fat solvent fixatives.
- Air embolism (gas):** Embolism of air bubbles.
- Septic embolism:** Embolism of pus-containing bacteria.
- Tissue embolism:** Embolism of small fragments of tissue.

- **Foreign body embolism:** Embolism of foreign materials such as talc and other small objects.
- **Amniotic fluid embolism:** Embolism of amniotic fluid, foetal cells, hair, or other debris that enters the mother's bloodstream via the placental bed of the uterus and triggers an allergic reaction; diagnostic morphologic feature is **amniotic debris** in the pulmonary capillaries.

Infarction

- **Infarction, MC** results from **occlusion of arterial supply**; rarely caused by obstruction of venous drainage, usually in organs having no bypass channels (**ovary, testis**).
- **Common to all infarctions is ischaemic coagulative necrosis**, but an **important exception** is encephalomalacia (infarcts in **brain**), which is marked by **liquefactive necrosis**.

Haemorrhagic (Red) Infarcts	Pale (white) Infarcts
Seen in venous occlusion (e.g. torsion of ovary, testis) and in tissues that are loose (e.g., lung) or have a double innervation (small intestine, lung).	White infarcts Occur in solid organs with end arteries (having few anastomoses) such as kidneys and spleen ("Spoilt White Kid! ")

Amyloid Protein	Precursor	Disease
AL	Ig light chain of plasma cells	Primary amyloidosis (multiple myeloma)
AA	SAA	Systemic (secondary) amyloidosis (2° = 2A's = AA)
Ab2M	Beta-2 microglobulin (MHC Class I protein)	Hemodialysis associated amyloidosis
ATTR	Transthyretin	Senile systemic amyloidosis (earlier called senile cardiac amyloidosis) Familial amyloid polyneuropathy
A-beta	A-beta precursor protein (APP)	Alzheimer's disease
ACal	Calcitonin	Medullary Carcinoma of thyroid (Endocrine amyloid)
AIAPP	Islet Amyloid Polypeptide	Type II diabetes (Endocrine amyloid)
AANF	ANP	Isolated atrial amyloidosis
APrP	Prion Protein	Misfolded Prion Protein disease
A-alpha	Fibrinogen	Familial Renal Amyloidosis
ACys	Cystatin	Cerebral amyloid angiopathy

Important MCQ Points in Amyloidosis

- **MC cause** of systemic/secondary **AA** amyloidosis is **rheumatoid arthritis** in **developed countries**; in **India** it is **TB**.
- **MC organ** involved in systemic/secondary **AA** amyloidosis is **kidney**.

Glomus Tumour (Glomangioma)

- This is a benign, **extremely painful tumour** of **modified smooth muscle cells** (glomus cells present in arteriovenous shunts—**Sucquet Hoyer anastomosis**).
- It arises from the glomus body, a **neuromyoarterial receptor** sensitive to temperature that regulates arteriolar flow.
- Receptors and their tumours are **MC** found beneath nail beds of **distal phalanges**.

Bacillary Angiomatosis

- Caused by **Bartonella henslae** or **B. quintana**.
- There is a **non-neoplastic proliferation of small blood vessels** in the skin, lymph nodes and visceral organs especially in persons with **immunodeficiency**.
- Treatment: **erythromycin**.

AMYLOIDOSIS

Amyloidosis is a group of diseases having in common the deposition of amyloid (a pathologic proteinaceous substance, deposited between cells in various tissues and organs of the body).

- **Carpal tunnel syndrome** may be a/w **Ab2M** amyloidosis
- **Most specific** and diagnostic physical finding in **AI** amyloidosis is **macroglossia**.
- Spleen in amyloidosis
 - **Sago Spleen:** Amyloid deposits limited to the **splenic follicles** giving rise to "**taploca-like**" granules on gross inspection.

- **Lardaceous Spleen:** Amyloid largely spares the follicles and is deposited in the **splenic pulp**.

Diagnosis of amyloidosis

- Best site for taking **biopsy in amyloidosis** is **abdominal fat aspirate** >> rectal biopsy.
- On **light microscopy**, amyloid seen as amorphous eosinophilic extracellular substance.
- On **electron microscopy**, **non-branching fibrils** of indefinite length and 7.5–10 microns diameter are seen.
- **X-ray crystallography** shows **cross-beta pleated** configuration.
- **Congo red** is a **specific stain** for amyloid; shows **apple-green** birefringence on polarizing microscopy.
- Amyloid is **PAS positive**
- **Thioflavin-S** used to stain amyloid in tissue - fluoresces under UV light.

ROSETTES IN PATHOLOGY

- In pathology, rosette refers to a halo or "spokes-of-a-wheel" arrangement of cells around a central lumen, especially in neoplasms of neuroblastic or neuroectodermal origin.

Type of rosette	Central lumen contains	Seen in
Homer-Wintersteiner rosette	Small cytoplasmic extensions from surrounding cells	Retinoblastoma Pinealoblastoma Medulloepithelioma
Homer-Wright rosette	Meshwork of fibres - ' neuropil ' (primitive neuronal processes)	Supratentorial PNETs Pinealoblastoma Retinoblastoma
True Ependymal rosette	Empty central lumen	Ependymoma Ependymoblastoma
Perivascular pseudorosette	Called 'pseudorosette' since the central structure is not actually formed by the tumor itself but instead represents an arrangement of cells around native non-neoplastic element	Medulloblastoma PNET Central neurocytoma Piloxyoid astrocytoma

MORE PATHOLOGY TOPICS

Mallory Hyaline

- These are aggregates of intermediate **cytokeratin prekeratin filaments** in the cytoplasm of hepatocytes resulting from hepatocyte injury.

- Also called **alcoholic hyaline** since **MC** seen in **alcoholic hepatitis**.
- It is cytokeratin CK8/18 positive

Mallory hyaline is also seen in

- Primary biliary cirrhosis
- Hepatocellular Ca
- Chronic cholestatic syndrome
- Focal nodular hyperplasia
- Indian childhood cirrhosis
- Wilson's disease
- Diabetes mellitus
- Morbid obesity, Jejunoileal bypass
- Non Alcoholic steatohepatitis (NASH)

Serum Alkaline Phosphatase (ALP)

- Derived from (**BLIP**), **Bone; Liver; Intestine; Placenta**.
- **Raised serum alkaline phosphatase** seen in (remember all these conditions):
 - **Increased Osteoblastic Bone conditions:** Paget's disease (Osteitis deformans), Osteogenic sarcoma, Metastatic bone tumour, Metabolic bone disease (Rickets; Osteomalacia), Hyperparathyroidism.
 - **Biliary obstruction:** intra/extrahepatic; Biliary cirrhosis.
 - **Intestine:** Ulcerative colitis, Crohn's disease.
 - **Placenta:** Late **pregnancy**
 - Others: Infectious mononucleosis, Temporal arteritis, sarcoidosis, amyloidosis, RA.
- Alkaline phosphatase from **liver and bone is distinguished by heat stability** at 56 deg. centigrade; **ALP from bone is heat labile**; ("**Bone burns, Liver lasts!**").

Raised Serum Acid Phosphatase

- **Metastatic Cancer of Prostate** – in prostate acid phosphatase activity is 100 times more than in any other tissue.
- Prostatitis, urinary retention.
- Gaucher's disease, Niemann Pick's disease.
- Metabolic bone disease (Paget's, osteomalacia).
- Haemolytic anaemia.
- Any cancer that has metastasized to bone.

Creatine Phosphokinase (Creatine Kinase, CK)

- **CK-MM:** skeletal muscle ("**Macho Man Muscular!**")
- **CK-MB:** Heart ("**My Beating Heart!**")
- **CK-BB:** Brain (also bowel infarction, neoplasms) ("**Blood Brain Barrier!**").

Increased CK

- Cardiac muscle damage: Myocardial Infarction, Myocarditis
- Skeletal muscle damage: Rhabdomyolysis, Myositis, Crush injury or trauma, Dermatomyositis or Polymyositis, Vigorous Exercise, Muscular Dystrophy, Malignant hyperthermia, Intramuscular injections.
- Brain damage: Seizure, Cerebrovascular Accident, Delirium tremens.
- Others: Acute renal failure, Myxedema, Pulmonary infarction, Pulmonary Embolus, Acute Aortic Dissection, Statin

More High Yield Points

Hunner's ulcer	Ulcerative Interstitial cystitis; MC in women.
Malakoplakia	A/w E.coli; affects urinary bladder (chronic cystitis); foamy histiocytes with intracytoplasmic inclusions called Michaelis-Gutmann bodies are seen - pathognomonic.
Kollocytosis	Vacuolation of superficial epithelial cells (<i>ballooning degeneration</i>) is characteristic of human papilloma virus (HPV) types 6 and 11 .
Erythroplasia of Queyrat	Paget's disease of penis ; Persistent rawness of the glans followed by cancer of the penis.
Crooke's hyaline change	Occurs within pituitary basophils , caused by the presence of elevated cortisol levels.
Sheehan's syndrome	hypopituitarism usually caused by infarction of the anterior pituitary; classically a/w obstetric/haemorrhagic shock; post partum pituitary necrosis .
'Hurthle cells'	(Askanazy cells, oxyphil cells, or oncocytes) seen in Hashimoto's thyroiditis - large granular eosinophilic cell derived from thyroid follicular epithelium by accumulation of mitochondria.
Plummer's disease	Toxic multinodular goiter, usually not ass. with exophthalmos.
"Orphan annle eyes".	Hyperchromatic empty nuclei devoid of nucleoli seen in Papillary Ca. of thyroid .
Waterhouse-Friderichsen syndrome	Overwhelming septicaemic infection seen in meningococcal meningitis . There is bilateral adrenal haemorrhage beginning in the medulla.
Zellballen	Well-differentiated neuroendocrine cells arranged in nests, seen in carotid body tumour (chemodectoma) .
Duret haemorrhages	Seen in transtentorial herniations due to tearing of feeding vessels.
Seen in perinatal ischemic brain injury	Ulegyria (thin gliotic gyri) and status marmoratus (neuronal loss and gliosis associated with aberrant and irregular myelin formation in the basal ganglia and thalamus).
Capillary telangiectasias	In the brain occur MC in the pons .
Pathologic findings in TB meningitis	Arachnoid fibrosis, hydrocephalus and obliterative endarteritis.
HIV (AIDS) encephalopathy	Presence of multinucleated giant cells see throughout the cortex and white matter, microglial nodules, white matter pallor and reactive gliosis.
AIDS neuropathy	MC is a distal symmetric painful sensory neuropathy .
Alzheimer's disease	Neurofibrillary tangles, neuritic plaques, amyloid angiopathy, granulovacuolar degeneration in pyramidal cells of hippocampus .
Pick disease	Cortical atrophy in frontal and temporal lobes , Pick bodies (intracytoplasmic).
Lewy bodies	Intracytoplasmic inclusions in Parkinson's disease .
Krabbe's disease	Deficiency of β-galactosidase , globoid cells may be seen.
Ito cell	Pericytes in the presinusoidal space, normally vitamin A storage cell , major source of excess collagen in cirrhosis, i.e. major cell type involved in liver fibrosis.
Neonatal hepatitis	Is a/w panlobular giant cell transformation .
Reye's syndrome	Jaundice is characteristically absent or minimal .
Primary biliary cirrhosis	Most important autoantibody in Is IgG antimitochondrial antibody (AMA) in 90% cases. Often the earliest symptom is pruritus .
Bush tea disease	Budd-Chiari syndrome resulting from ingestion of herbal tea containing pyrrolizidine alkaloids.
Gaucher's cell	Foamy macrophage distended with PAS-positive material that has a fibrillary appearance resembling crumpled tissue paper .
Gandy - Gamna bodies	Seen in congestive splenomegaly - areas of fibrosis containing deposits of iron and calcium salts encrusted on connective tissue and elastic fibres.

Contd

Contd

Carbon monoxide poisoning	Bilateral necrosis of globus pallidus .
Methanol poisoning	Selective bilateral putaminal necrosis .
Chronic ethanol abuse	Bergman gliosis (due to Purkinje cell loss).
Kussakoff's psychosis	(Thiamine, vit B1 deficiency) foci of hemorrhages in the mammillary bodies are prominent.
"Wire loops"	Seen in Class IV lupus nephritis (diffuse proliferative GN) . They are immune complex deposits, typically subendothelial ; most severe form of lupus nephritis carrying worst prognosis. Wire loops are also seen in (HIV)-associated nephropathy.
Hematoxylin bodies	Disordered nuclei of cells damaged by autoantibodies are specific to SLE .
Cat-scratch disease	Rounded or stellate granuloma .
Pneumoma bodies	
Ames test	A simple in vitro test for carcinogenicity utilising the ability of potential carcinogens to induce mutation in selected strains of the bacterium Salmonella typhimurium .
Exfoliative cytology	MC used in diagnosis of dysplasia, Ca in situ, and invasive cancer of the cervix and also tumours of the stomach, bronchus and urinary bladder.
Diseases due to defects in DNA repair:	Xeroderma pigmentosum; Bloom's syndrome; Ataxia telangiectasia; Fanconi's anemia.
Dubin-Johnson Syndrome	A cardinal feature of is the accumulation in the lysosomes of centrilobular hepatocytes of dark, coarsely granular pigment - the liver may be grossly black in appearance !! This pigment is thought to be derived from epinephrine metabolites that are not excreted normally.

PATHOLOGIC BODIES AND CELLS

Body/sign/clue	Features	Diagnosis
Antoni A tissue	Densely cellular areas with palisaded nuclei, fascicles and Verocay bodies	Schwannoma
Antoni B tissue	Loose, gelatinous stroma, fewer cells, microcystic changes	Schwannoma
Arran Perkins bodies	Elastin bodies in connective tissues streamers below vellus follicles	Androgenic alopecia
Asteroid bodies	Star-like cytoplasmic inclusions in giant cells	Sarcoidosis and other granulomatous disease (TB, botryomycosis, sporotrichosis, actinomycosis, leprosy, foreign body granuloma, berylliosis)
Azopardi effect	Basophilic vascular streaking (encrusted nuclear material/DNS around vessels)	Tumor necrosis, crush
Banana bodies	1. Curvilinear, membrane bound bodies in Schwann cells on EM 2. Crescentic, ocher bodies in the dermis	1. Farber disease 2. Ochronosis
Beanbag cells	Large macrophages demonstrating cytophagocytosis	Subcutaneous panniculitis-like T-cell lymphoma/ cytophagic histiocytic panniculitis
Birbeck granules	Tennis racket structures on EM	Langerhans cells
Bull's Dermis		GA, interstitial granulomatous dermatitis, resolving vasculitis, folliculitis, early KS, desmoplastic MM, chronic photodermatitis, breast CA mets
Campary Joseph spaces	Clefts at DEJ associated with basal layer injury, a.k.a. Max-Joseph cleft	LP, lichen nitidus
Caterpillar bodies	Eosinophilic, segmented, elongated (epidermal) bodies on roof of blisters (Col IV)	Porphyrias

Contd...

Contd...

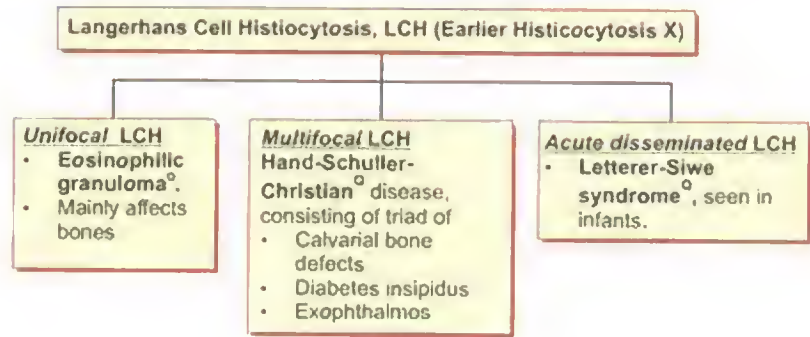
Body/sign/clue	Features	Diagnosis
Cholesterol clefts	Needle-like crystals	Sclerema neonatorum, subcutaneous fat necrosis of the newborn (may have more inflammation and calcification than sclerema), post-steroid panniculitis, NXG, cholesterol emboli, NLD, trichilemmal cyst
Chunks of coal	Large atypical lymphoid cells with hyperchromatic nuclei	Lymphomatoid papulosis
Cigar bodies	Oval, elongated yeast cells	Sporotrichosis
Colloid/Civatte	Apoptotic bodies in epidermis	Lichen planus and variants
Comma-shaped bodies	Cytoplasmic worm-like bodies on EM	Benign cephalic histiocytosis
Conchoidal bodies (Schaumann bodies)	Shell-like, lamellated, basophilic, calcified protein complexes in giant cells	Sarcoidosis and other granulomatous diseases
Corps grains	Small, dyskeratotic, acantholytic keratinocytes with elongated grain-shaped nuclei seen in stratum corneum	Darier disease, Grover, warty dyskeratoma,
Corps ronds	Enlarged, dyskeratotic, acantholytic keratinocytes with round nuclei and perinuclear halo seen in Malpighian layer and surrounding basophilic dyskeratotic material	Darier disease, Grover, warty dyskeratoma,
Councilman bodies	Cytoplasmic inclusion	Viral hepatitis; Yellow fever
Cytoid bodies	Heterogeneous round, oval, or polygonal deposits, usually in dermis	Collective form for colloid bodies, Russell bodies, amyloid, elastic globes
Donovan bodies	Single or clustered rod safety pin like bacteria in macrophages	Granuloma Inguinale
Dutcher bodies	Intranuclear pseudoinclusions in malignant plasma cells, Ig	B-cell lymphoma, multiple myeloma
Farber bodies	Comma-shaped tubular structures in cytoplasm of fibroblasts	Farber disease
Flame figures	Poorly circumscribed, small areas of amorphous eosinophilic material adherent to dermal collagen	Eosinophilic cellulitis + flame figures = Wells' syndrome > arthropod bites, parasites, BP, DH, eosinophilic panniculitis
Floret cells	Multinucleated giant cells with marginally placed nuclei	Pleomorphic (spindle cell) lipoma
Flower cells	Atypical CD4+ T cells, prominent nuclear lobation	HTLV-1, ATL
Ghost cells	Calcified necrotic anucleate adipocytes with thickened membrane	Pleomorphic panniculitis (+saponification) (vs. shadow/ghost cells in pilomatricoma)
Giant granules in neutrophils	Large granules	Chediak-Higashi
Globi	Globular clumps of AFB in macrophages (foam/lepra/virchow)	Lepromatous leprosy
Guarnieri bodies	Cytoplasmic, eosinophilic inclusion in keratinocytes	Smallpox, vaccinia
Henderson-Patterson bodies	Large, cytoplasmic, eosinophilic inclusions in keratinocytes	Molluscum contagiosum

Contd

thl

Body/sign/clue	Features	Diagnosis
Homer Wright Rosettes	Central nerve fibrils, peripheral small tumor cells	Cutaneous neuroblastoma
Horan's anomaly	Vacuolated leukocytes on peripheral smear	Dorfman-Chanarin
Imkin bodies	Eosinophilic globules at DEJ made of BMZ components	Spietz nevus
Lafora bodies	Concentric amyloid deposits (=polyglucosan bodies)	Lafora disease
Lipofuscin-like granules	Yellow-brown granules in dermal macrophages	Amiodarone hyperpigmentation
Maquie sign	Organisms at the periphery of macrophages	Leishmania
Mallory/sclerotic bodies	Muriform cells, "copper pennies," round thick-walled brown fungi	Chromoblastomycosis
Michaelis Gutman bodies	Calcified, degraded bacteria in macrophages, lamellated	Malakoplakia
Mikulicz cells	Large macrophages containing klebsiella rhinoscleromatis	Rhinoscleroma
Morulae	Leukocyte intracytoplasmic inclusions, Ehrlichia multiplying in cell vacuoles	Ehrlichiosis
Mulberry bodies	Dermal mulberry-like endospore/ sporangia	Protothecosis (vs. "mulberry-like figures" on EM in Fabry eccrine glands)
Mulberry cells	Moruloid, granular, eosinophilic adipocytes - "ping pong balls"	Hibernoma
Negri bodies	Eosinophilic, cytoplasmic inclusions in neurons	Rabies
Orphan bodies	Small, lamellated granules rich in lipids in granular layer, membrane coating granules on EM	Important for permeability barrier, absent in harlequin fetus
Onion skinning	Perivascular, hyaline material	Lipoid proteinosis (onion skin fibrosis in GF, angiofibroma)
Pautrier microabscesses	Three or more atypical lymphocytes with epidermis	Mycosis fungoides
Pohl Pinkus Marks	Isolated hair shaft narrowing (severe=bayonet hair)	Surgery/trauma
Pseudomoma bodies	Concentrically laminated, round calcified bodies	Papillary Ca thyroid, Serous cystadenoma of ovary, Meningioma, Malignant Mesothelioma, "PSaMMoma"
Pustule ovoid bodies of Millan	Large eosinophilic granules with clear halo	Granular cell tumor
Russell bodies	Immunoglobulin deposits in plasma cells	Rhinoscleroma, plasmacytosis
Spiderweb cells	Globular, striated, vacuolated cells	Adult rhabdomyoma
Splendore-Hoeppli deposits	Flame figure-like eosinophilic deposits around organisms	Parasites, fungus, bacteria
Verrucous bodies	Palisading nuclei in rows around eosinophilic cytoplasm	Schwannoma
Weibel Palade	Dense rod or oval organelles on EM	Endothelial cells

Langerhans Cell Histiocytosis (Earlier Called Histiocytosis X)



EXTRA EDGE

- Langerhans cell is **CD1a and S-100** positive; **Birbeck granules** (tennis rackets) on electron microscopy are characteristic.

INTRANEURONAL INCLUSION BODIES

1. **Pick bodies:** Pick disease.
2. **Lewy bodies:** Classic (brain stem) Lewy bodies are seen in Parkinson disease, and cortical lewy bodies are noted in dementia with Lewy body disease.
3. **Hirano bodies:** commonly seen in the hippocampus and are particularly numerous in Alzheimer disease (AD).
4. **Bunina bodies:** in motor neurons in cases of familial and sporadic amyotrophic lateral sclerosis.
5. **Marinesco bodies:** located chiefly in melanin containing brain stem neurons; no known pathologic significance.
6. **Lafora bodies:** found in large numbers in myoclonic epilepsy, particularly in the dentate nucleus.

More One Liners

- **Kimura's disease** = enlarged lymph nodes of head and neck and salivary glands.

- **Kikuchi's disease** = Histiocytic necrotizing lymphadenitis of cervical region, MC in Orientals.
- **Polymorphonuclear leukocytes** are **rapidly recruited** from the bone marrow, localize at the wound site by binding to activated endothelium and invade the wound site within the first day.
- **Castleman disease** = Angiofollicular lymph node hyperplasia; **"Lollipop" bodies** are seen in **hyaline vascular variant** of Castleman's disease.
- **Emperipolesis:** It is defined as, "the active penetration of one cell by another which remains intact". It differs from phagocytosis because - the engulfed cell exists within another cell, remains viable, and can exit with no physiological and morphological consequence for either of them !! Seen in:
 - **Rosai Dorfman disease** (sinus histiocytosis with massive lymphadenopathy)
 - **Myelodysplastic syndrome**
- **Neutrophils Extracellular Traps (NETs)** are extracellular fibrillar networks that concentrate antimicrobial substances at sites of infection and prevent the spread of microbes by trapping them in the fibrils.
- In **flow cytometry**, **forward scatter** is directly related to **cell size** and **side scatter** to **granularity**.

FIXATIVES IN PATHOLOGY

Fixative	Use
10% Neutral buffered formalin (NBF - buffered by Phosphate)	Most widely used formaldehyde-based fixative for routine histopathology
Paraformaldehyde	Best fixative for perfusion ; must be prepared fresh Can be used with glutaraldehyde for electron microscopy
Zenker's fixative	Lymphohematopoietic tissues Eyes

Contd

Contd

Fixative	Use
Glutaraldehyde	Electron microscopy
Michel's fixative	Immunofluorescence
Helly's fixative	Bone marrow Extramedullary haematopoiesis Intercalated discs of cardiac muscle.
B5 fixative	Lymphohematopoietic tissue recommended for IHC.
Born's solution	GIT biopsies Endocrine gland tissue Testes
Hollande's	GIT biopsies Endocrine gland tissue
Gendre's solution	For the preservation of glycogen and other carbohydrates.
Alcoholic formalin	Can be used for fixation or post-fixation of large fatty specimens (particularly breast).

STAINS

Stain	Target (Material Identified)
Pigments and minerals	
von Kossa stain and Alizarin Red S	Calcium
Hall's stain	Bilirubin
Ilohexamine, Rubeanic acid	Copper stains for Copper (in Wilson's disease)
Prussian Blue, Perl's iron	Iron, (hemosiderin in iron overload)
Turnbull's blue	Ferrous iron in tissue
Sudan Black B (for lipochrome)	Lipofuscins
Gomori's methenamine silver	Urate crystals
Pontana Masson Silver method	Argentaffin granules (in carcinoid tumors) Dubin Johnson pigment Melanin (malignant melanoma)
Carbohydrates	
Alcian Blue	Acid mucopolysachharides, acetic mucin
Colloidal iron	Mucopolysachharides
Congo Red	Amyloid
Thioflavin S	Amyloid deposits in tissue
Mucicarmine	Mucin
PAS (Periodic Acid Schiff)	Glycogen Fungus
PAS D (PAS with diastase)	Detects glycogen by digesting out sugars followed by PAS staining
Lipids	
Oil Red O	Fat (in Frozen section)
Sudan Black B	Fat
Microorganisms	
Ziehl-Neelsen's; Kinyoun	Identification of acid fast bacilli (<i>Mycobacterium TB</i> , <i>Mycobacterium Lepae</i> , <i>Nocardia</i>)

Contd...

Contd...

Stain	Target (Material Identified)
Fite's Faraco stain	Mycobacterium <i>Leprae</i>
Auramine Rhodamine stain	Mycobacterium TB
Warthin Starry silver stain, Steiner and Steiner (silver) method	<i>Spirachetes</i>
Giemsa stain	H.pylori in tissue
Modified Giemsa (May-Greunwald)	H.pylori in blood, lymph nodes
Gridley's stain for ameba	Eosin stained Ingested erythrocytes in <i>ameba</i>
Shikata Orcein stain and Victoria Blue stain	Hepatitis B surface antigen (<i>HbSAg</i>)
India ink stain	<i>Cryptococcus</i>
Dienes's stain	Mycoplasma
Calcofluor white	Stains <i>cellulase and chitin</i> in fungi, algae and plants
Fonatana's (for films) and Levaditis (for tissue sections) stains	<i>T.pallidum</i>
Grocott's Methenamine silver	<i>P.jiravecil</i> , Fungi
PAS (Periodic Acid Schiff)	Tryphorema <i>whippelli</i>
Nervous tissue	
Bielchowsky silver stain; Modified thioflavin's stain	Neurofibrillary tangles
Bodian's method	Nerve fibres
Holzer's stain	<i>Glial</i> fibres
Hortega stain	<i>Pineal</i> gland
Cresyl violet (Nissl) stain	<i>Nissl substance</i> in cytoplasm of neurons
Luxol's fast blue	<i>Myelin/myelinated</i> axons
Other tissues and cells	
Hematoxylin and Eosin	MC used stain in medicine—nucleus stains <u>b</u> lue (<u>b</u> asophilic) and others are stained red
Toulidine blue stain	Mast cells ; <i>metachromatic</i> granules
Tartarate resistant acid phsophatase	Hairy cells in Hairy cell leukemia;
Grimelius, Pascal, Churukian Schenk (argyrophil stains)	Carcinoid tumor
Quinacrine stain	Q banding in <i>chromosome staining</i>
Giemsa	G banding in <i>chromosome staining</i> (MC used method for chromosomes)
Fluorescein	Stains carneal strama - used for detecting abrasians / epithelial defects
Rose Bengal	Stains devitalised epithelial cells (lacking mucin) - used for dry eyes
Ki-67 stain (immunohistochemical)	For dividing tumor cells
Movat pentachrome stain (5 combined stains!)	To assess vascular remodeling in pulmonary or CVS pathology Also excellent for evaluating long-standing collagenous fibrosis and for distinguishing advanced fibrosis from more recent fibroplasia.
Connective tissue	
Verhoeff Van Gieson stain; Weigert's resorcin Fuchsin stain; Orcein stain	Elastin fibres
Fraser Lendrum method	Fibrin

Contd

Contd

Stain	Target (Material Identified)
Jones silver stain	Basement membrane of glomerulus of <i>kidney</i>
Phosphotungstic acid hematoxylin (PTAH, mallory) stain	Muscle crass striations and fibrin For demonstrating contraction band necrasls of MI
Gordon and Sweet's Reticulin stain	Reticular fibres (esp. in liver pathology) Identifies collagen type 3
Masson's Trichrome stain,	Identifies collagen type 1 Staging of chronic hepatitis; Distinguishes collagen from muscle in tissue specimens
Masson's Trichrome stain,	Identifies collagen type 1
Proteins and Nucleic Acids	
Methyl Green Pyronin (MGP) stain	Stains DNA green and RNA red
Feulgen stain	Stains only DNA

CRISPR

- "CRISPR" stands for **Clustered Regularly Interspaced Short Palindromic Repeats**.
- CRISPRs are the hallmark of the **bacterial immune system**, defending against invading viruses.
- CRISPR are *sections of genetic code* containing short repetitions of base sequences followed by *spacer DNA segments*.
- The CRISPR-Cas9 system consists of two key molecules that introduce a mutaton in the DNA - an **endonuclease enzyme (cas-9)** and the **guide RNA**.
- Identified **first in archaea** and later in bacteria, short nucleic acid sequences are captured from invading pathogens and integrated in the CRISPR loci amidst the repeats. Small RNAs, produced by transcription of these loci, can then guide a set of endonucleases to cleave the genomes of future invading pathogens, thereby disabling their attacks.
- **CRISPR-Cas9** is used in **genome editing technology**.

EXTRA EDGE

- As the number (gauge, G) of the cannula increases, the diameter decreases and the flow rate decreases.
- Mnemonic: Start at 14 and keep adding 2 (except at 16, you add 1); see table and picture mnemonic (For 14, imagine the core of the earth with Orange lava as mentioned above and move outward)



Fig. 10.5: Picture Mnemonic for IV Cannulae

COLOR CODES OF BLOOD COLLECTION TUBES

- The **vacuum tube method** is the ideal method for collecting blood from antecubital veins. A **Vacutainer** (developed by Joseph Kleiner; marketed by Becton Dickinson) is a commercially available blood collection tube - it is a sterile glass tube with a **colored rubber stopper** creating a vacuum seal inside of the tube facilitating the withdrawing of a **predetermined volume of blood**.

COLOR CODES AND Mnemonic for IV Cannulae

Gauge	Color	Mnemonic (see picture)
14 G	Orange	Orange lava in the core of the earth
16 G	Grey	Grey soil on the surface of the earth
17 G	White	White water put to soil
18 G	Green	Green grass grows
20 G	Pink	Pink flowers grow above it
22 G	Blue	Blue sky above
24 G	Yellow	Yellow sun shining
26 G	Violet	

- Vacutainer tubes may **contain additives** designed to stabilize and preserve the specimen prior to analytical testing.
- As a general rule blood samples should be drawn in the following order ("**Order of Draw**") to **avoid cross contamination of additives** between the tubes.
 1. Sterile tubes for Blood Culture (Yellow)
 2. Light blue
 3. Red
 4. Green
 5. Lavender
 6. Grey
 - Mnemonic: "She Likes Really Good Loving Guys"

Cap Color	Additive	Use/Comments
Containers containing coagulants		
Gold	Clot activator and gel	Serum separator tube for serum determinations: Immunology and virology assays
Orange (tiger top)	Thrombin	For stat serum testing
Red (plastic tube)	Clot activator (NO gel)	For stat serum testing
Containers containing anti-coagulants		
Gray	Fluoride; oxalate; iodoacetate (glycolytic inhibitors)	For glucose, lactate, alcohol and bicarbonate determinations
Green	Lithium heparin	For plasma determinations: for arterial blood gases, ammonia, urea and electrolytes
Lavender	EDTA	For whole blood hematology determinations - Full blood count, ESR, HbA1C; molecular genetic studies
Light blue	Sodium citrate	For coagulation assays- INR, D-dimer, fibrinogen
Others		
Red (glass)	None	
Light Yellow	Sodium polyanethol sulfonate	Blood culture, HLA phenotyping
Brown	EDTA or heparin	Lead determinations

Note

- All important topics in general pathology have been covered here.
- Genetics has been covered in a separate chapter.
- CNS, CVS, GIT, Liver and other individual system pathologies have been covered under respective "systems" in Medicine and Surgery Chapters.
- Pathology related to "Neoplasia" has been covered under Oncology chapter.

CHAPTER

11

Hematology

PHYSIOLOGY OF BLOOD

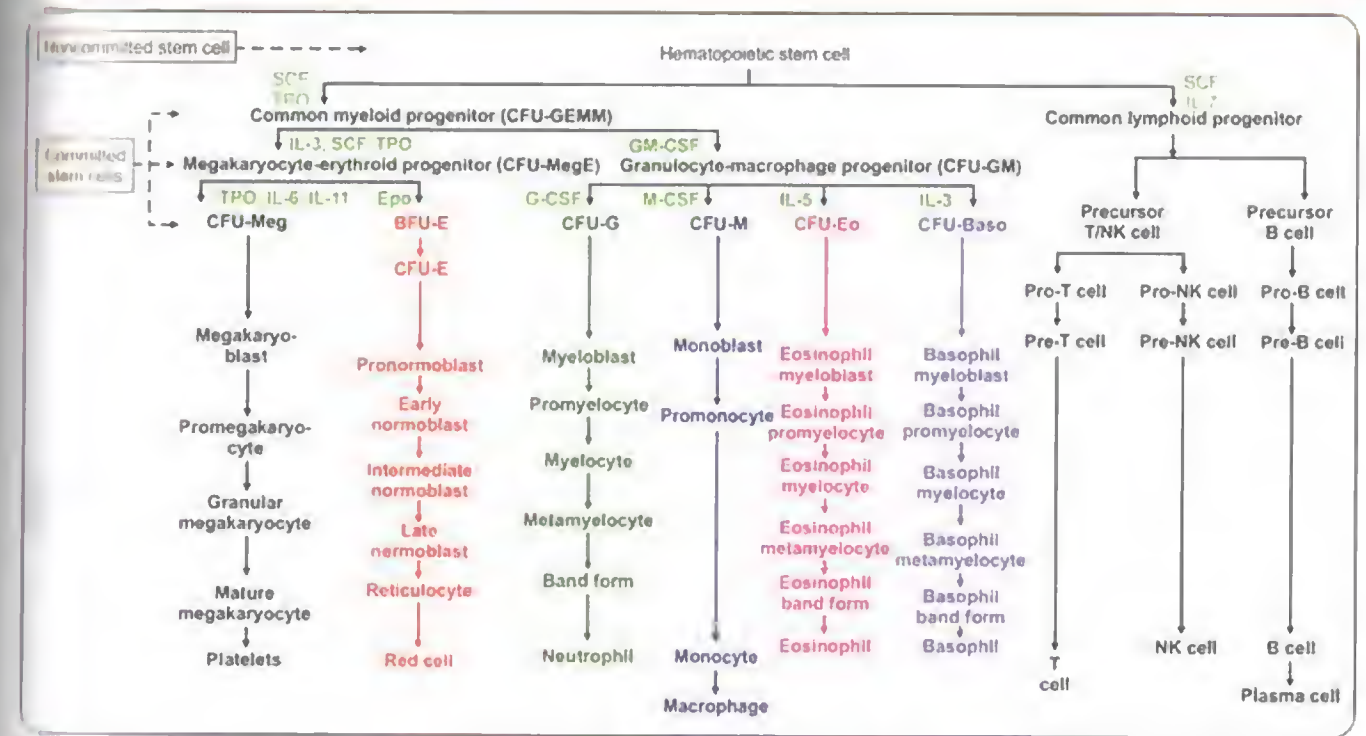


Fig. 11.1: Normal hematopoiesis. Abbreviations: SCF: Stem cell factor; TPO: Thrombopoietin; IL: Interleukin; EPO: Erythropoietin; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte-macrophage colony stimulating factor; M-CSF: Macrophage colony stimulating factor; CFU-GEMM: Colony forming unit-Granulocyte Erythroid Megakaryocyte Macrophage; CFU-GM: Colony forming unit-Granulocyte Macrophage; CFU-MegE: Colony forming unit-Megakaryocyte Erythroid; BFU-E: Burst forming unit-Erythroid; CFU-E: Colony forming unit-Erythroid; CFU-G: Colony forming unit-Granulocyte; CFU-M: Colony forming unit-Macrophage; CFU-Eo: Colony forming unit Eosinophil; CFU-Baso: Colony forming unit-Basophil; NK: Natural killer

EXTRA EDGE

- In the above figure, pronormoblast = proerythroblast; early normoblast = basophilic erythroblast; intermediate normoblast = polychromatic erythroblast; late normoblast = orthochromatic erythroblast.
- **Largest cell is proerythroblast.**
- **Hemoglobin** appears at the stage of **intermediate normoblast**
- Mitosis occurs up to the stage of **intermediate normoblast** and **mitosis** is most active at this stage.

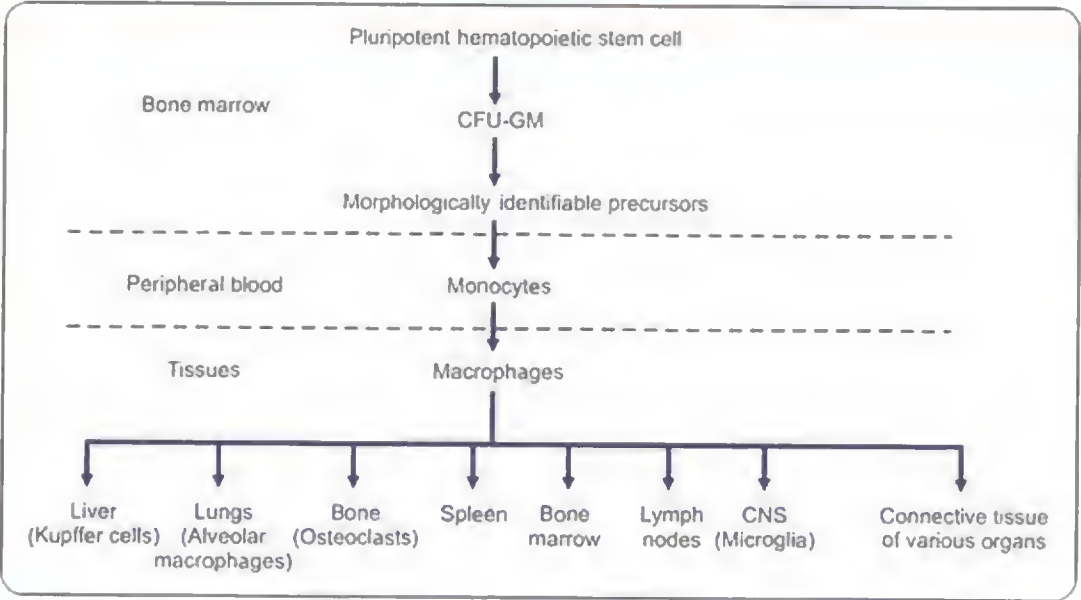


Fig. 11.2: The mononuclear phagocyte system

EXTRA EDGE

- In addition to above some special types of macrophages are in following locations:
 - Tissues - Macrophages
 - Blood - Monocytes
 - Placenta - Hofbauer cells
 - Connective tissues - Histiocytes
 - Kidney - Mesangial cell
 - Lymphoid follicles - Tingible body macrophage
 - Site of inflammation: epithelioid cell, multinucleated giant cell (Langhan's cell - NOT Langerhans)

EVALUATION OF ANEMIAS

RBC Indices

Index	Normal value
Mean cell volume (MCV) = (hematocrit \times 10)/(red cell count \times 10 ⁶)	82–98 fL (femtoliter)
Mean cell hemoglobin (MCH) = (hemoglobin \times 10)/(red cell count \times 10 ⁶)	27–33 pg (picograms)
Mean cell hemoglobin concentration (MCHC) = (hemoglobin \times 10)/hematocrit, or MCH/MCV	31–35 g/dL or %

EXTRA EDGE

- (**MCV** reflects iron deficiency **more accurately** than MCH, MCHC or PCV).

Red Cell Distribution Width (RDW)

- RDW = degree of *variation of red cell size* = a measure of 'anisocytosis'.
- Normal RDW = 11.5–14.5

Low MCV with Normal RDW	Low MCV with High RDW
Thalassemia carrier/trait (Includes <i>beta thalassemia minor, heterozygous thalassemia</i>)	Iron deficiency anemia Sickle cell -beta thalassemia Hemoglobin H disease

Packed Cell Volume (PCV) or Hematocrit

- It is the proportion of blood volume that is occupied by RBCs.
- Normal values are about **45% for men** and about **42% for women**.

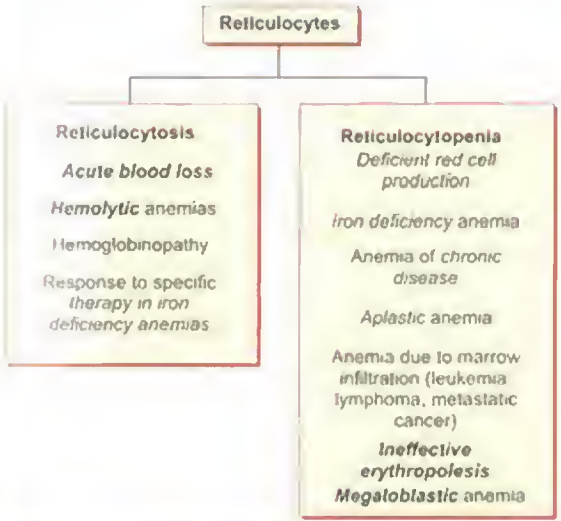
Erythrocyte Sedimentation Rate

- **Raised ESR:** Infections; Inflammation (e.g. temporal arteritis); Cancer; Pregnancy; SLE
- **Decreased ESR:** Sickle cell; Polycythemia; CHD (unknown).

Reticulocytes

- Reticulocytes are **polychromatic** red cells that have been **recently/prematurely released** from the bone marrow.
- They are slightly **larger than normal** and **grayish blue** in color with **blue or black punctate spots** on staining

with the *supravital* stains (**Wright-Giemsa, methylene blue** or **brilliant cresyl blue**) - their color represents residual amounts of **ribosomal RNA**.
These cells appear in circulation
➤ In response to **erythropoietin stimulation** or
➤ In response to architectural **damage of the bone marrow** (fibrosis, infiltration of the marrow by malignant cells, etc.) that results in their disordered release from the marrow.
Normal reticulocyte count = **1 to 2% of RBCs**.
A **corrected reticulocyte count** provides a reliable measure of effective red cell production.
A **reticulocyte production index**
➤ > 2.5 indicates **hemolysis** (blood loss, intravascular hemolysis, RBC membrane abnormality, hemoglobinopathy, immune destruction)
➤ < 2 indicates either a **hypoproliferative anemia** or **maturation disorder** (iron deficiency, thalassemia, vitamin B12/folate deficiency, aplasia, drug toxicity).



Methods to correct the reticulocyte count for the degree of anemia

- Reticulocyte count = % of reticulocytes in RBC population.
 - **Corrected Reticulocyte count** = % of reticulocytes \times (patient's Hct/45)
 - Reticulocyte production Index = Corrected Reticulocyte count / maturation time in peripheral blood in days (Normal values of all the above is 0.5–1.5%)
 - Corrected Reticulocyte count = % of reticulocytes \times RBC count/L³
(Normal values for absolute reticulocyte count are from 25–75 \times 10⁹/L)
- Note: Reticulocyte maturation time = 1 day for Hct > 40%; 1.5 days for Hct 30–40%; 2 days for Hct 20–30% and 2.5 days for Hct < 20%.

Tests of Iron Supply and Body Iron Storage

- **Serum iron**
 - Normal serum iron = 9 to 27 μ mol/L (50–150 μ g/dL).
- **Serum ferritin.**
- **Serum Ferritin** is a **nonheme iron containing protein**:
 - It is the **Best indicator of body iron stores**.
 - Normal (adult male) = ~100 μ g/L.
 - Normal (adult female) = 30 μ g/L.
 - Serum ferritin is also an **acute-phase reactant** and, in the presence of acute or chronic inflammation, may rise several-fold above baseline levels.
- **Total iron-binding capacity (TIBC)**
 - TIBC is an **indirect measure** of serum transferrin
 - Normal TIBC is 54–64 μ mol/L (300–360 μ g/dL).
- **Percent transferrin saturation (PTS)**
 - PTS = serum iron level (\times 100) / TIBC.
 - Normal PTS = 25 to 50%.
 - A **diurnal variation** in the serum iron leads to this variation.
 - Iron deficiency states are associated with saturation levels below 20%.
- **Red Cell protoporphyrin levels**
 - Normal = < 30 μ g/dL of RBCs
 - If > 100 μ g/dL of RBCs- it indicates iron deficiency or lead poisoning.

Common Red Cell Appearances and their Causes

Microcytosis (reduced average cell size, MCV < 80 fL)	<ul style="list-style-type: none">• Iron deficiency anemia• Sideroblastic anemia• Thalassemia• Pyridoxine deficiency• Lead poisoning• Copper deficiency• Also Anemia of chronic inflammation (BUT more commonly presents as normocytic anemia)
Macrocytosis (increased average cell size, MCV > 100 fL)	<ul style="list-style-type: none">• See below
Target cells (central area of Hb)	<ul style="list-style-type: none">• HbC disease• Asplenia (Post-splenectomy)• Liver disease• Thalassemia• "HALT and aim for the Target"
Spherocytes (dense cells, no area of central pallor)	<ul style="list-style-type: none">• Hereditary spherocytosis• Autoimmune hemolysis• Postsplenectomy• Disseminated intravascular coagulation (DIC)

Contd...

Contd...

- Nucleated red blood cells (normoblasts)**
 - Marrow infiltration
 - Myelofibrosis
 - Severe hemolysis
- Howell-Jolly bodies (small round nuclear remnants)**
 - Post-splenectomy
 - Hyposplenism
 - Dyshemopoiesis
- Polychromasia (young red cells-reticulocytes present)**
 - Hemolysis
 - Increased red cell turnover
- Basophilic stippling (abnormal ribosomes appear as blue dots)**
 - Thalassemia
 - Anemia of chronic disease
 - Iron deficiency
 - Lead poisoning
 - "TAIL"

Contd...

- Helmet cell, Schistocyte**
 - DIC
 - Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP)
- Burr cell**
 - HUS/TTP
- Poikilocytes**
 - Nonuniform shapes in HUS/TTP, microvascular damage, DIC
- Teardrop cell**
 - Myeloid metaplasia with myelofibrosis
- Bite cell**
 - G6PD deficiency

Contd...

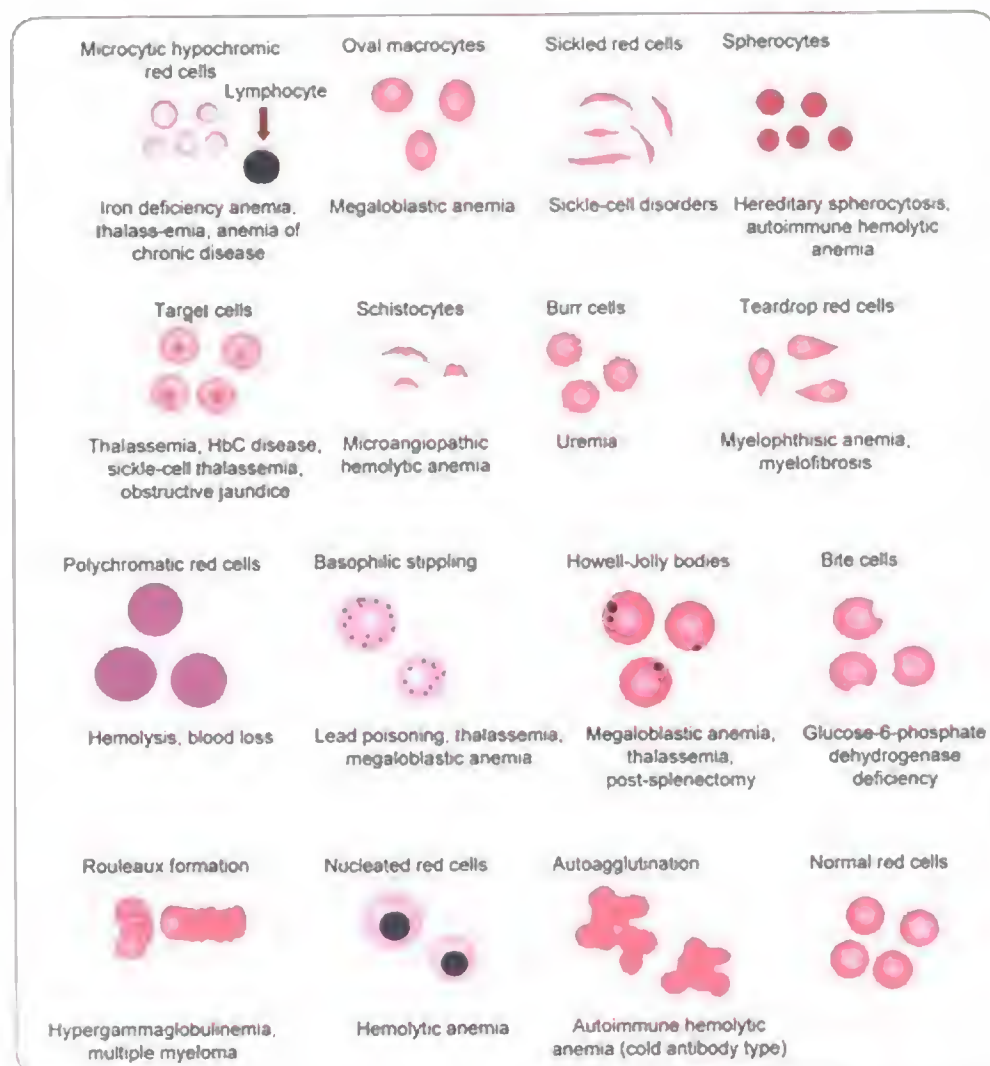


Fig. 11.1 Morphological abnormalities of red cells in different types of anemias. Size of red cells is compared with the nucleus of a small lymphocyte (1/100).

IRON DEFICIENCY ANEMIA

Iron Metabolism Essentials

- Iron absorption** takes place largely in the proximal small intestine (duodenum and jejunum).
- Each milliliter of red cells contains 1 mg of elemental iron.
- Iron is absorbed in the **ferrous** form.
- Most of the iron is deposited in the enterocytes as **ferritin**.
- Iron absorption is regulated according to the demand, i.e. when there is iron deficiency absorption increases.
- The principal **iron regulatory hormone is hepcidin** (liver derived peptide) that normally **inhibits iron absorption**.
- In **iron deficiency, hepcidin levels are also low** and iron is much more efficiently absorbed.
- Iron is transported in the blood in combination with a glycoprotein **transferrin**.
- Iron is stored as **ferritin** (in **ferric** form).
- Iron is stored** in **reticuloendothelial cells** of **liver, spleen and bone marrow**.
- Iron deficiency anemia** is the MC anemia followed by the **anemia of inflammation**.
- The average **red cell lifespan** is **120 days**.
- Lifespan of **fetal RBCs** and **term neonatal RBCs** is about **80 days**.
- Lifespan of **premature neonate RBCs** - **40-60 days**.

Factors Influencing Iron Absorption

- Decreased absorption**
 - By complexing with iron: **phytate, phosphate, milk, EDTA, tetracycline**
 - By opposing reduction of ferrous to ferric form: Antacids, alkalis, pancreatic secretions.
- Increased absorption**
 - By enhancing reduction of ferrous to ferric form: **Ascorbic acid, HCl**, gastric secretions, citric acid.

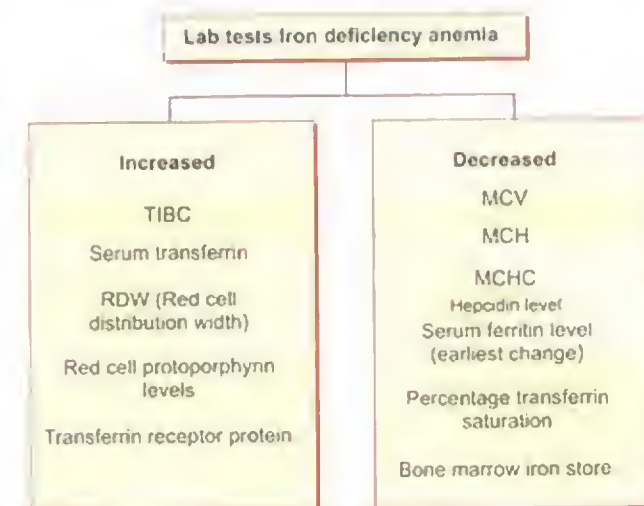
Causes of Iron Deficiency

- Increased Demand for Iron**
 - Rapid growth in infancy or adolescence
 - Pregnancy and lactation
 - Erythropoietin therapy
- Increased Iron Loss**
 - Acute and Chronic blood loss:
 - GI (peptic ulcer, hemorrhoids, NSAIDs, **hookworm** infestation, Ca colon)
 - Uterine (menorrhagia, malignancies, Menses)
 - Urinary tract: hematuria, malignancy, **chronic dialysis** in renal failure
 - Blood donation
 - Phlebotomy as treatment for polycythemia vera.
- Decreased Iron Intake or Absorption**
 - Malabsorption** from disease (**sprue, Crohn's disease**)

- Malabsorption from **surgery** (**gastrectomy** and some forms of bariatric surgery)
- Acute or chronic **inflammation**.

Blood Investigations

- Microcytic hypochromic anemia** (**Microcytosis precedes hypochromia**)
- Poikilocytosis in the form of **pencil cells, target cells and ring/pessary cells** may be seen
- There may be **thrombocytosis**
- Bone marrow is **hypercellular** with **erythroid hyperplasia**. Depleted bone marrow iron detected by **Prussian blue** staining. Bone marrow iron decreases **earlier than** serum iron.



Differential Diagnosis of Anemias

Tests	Iron deficiency	Thalassemia	Inflammation (Chronic disease)	Sideroblastic
Serum Iron	↓	N or ↑	↓	↑
Serum ferritin	↓	N	N or ↑	↑
TIBC (transferrin)	↑	N	↓	N
Morphology	Microcytic, hypochromic	Microcytic, hypochromic	Normocytic normochromic	Variable, Ringed sideroblasts

EXTRA EDGE

- Mentzer index** = MCV/RBC count; < 13 in thalassemia; > 13 in the rest of above.

Treatment

- **Elemental iron content** of 325 mg tablets of various compositions is given below
 - Ferrrous sulphate: 65 mg
 - Ferrrous fumarate: 107 mg
 - Ferrrous gluconate: 39 mg
 - For iron replacement therapy, up to **200 mg of elemental iron per day** is given, usually as three or four iron tablets (each containing 50-65 mg elemental iron) given over the course of the day.
- Oral iron preparations should be taken on an **empty stomach**, since **food may inhibit iron absorption**.
- **Vitamin C tablet administration before taking oral iron may improve iron absorption.**
- A dose of 200 mg of elemental iron per day should result in the **absorption of iron up to 50 mg/d.**
- The goal of therapy in iron-deficiency anemia is not only to repair the anemia, but also to provide stores of at least **0.5-1 g of iron. Sustained treatment** for a period

- of **6-12 months after correction of the anemia** will be necessary to achieve this.
- Earliest hematological response to iron therapy is evidenced by **reticulocytosis** which begins to increase within **4-7 days** after starting therapy and **peaks at 7-10 days.**
- Of the **complications of oral iron therapy**, **gastrointestinal distress** is the most prominent (abdominal pain, nausea, vomiting, or constipation).

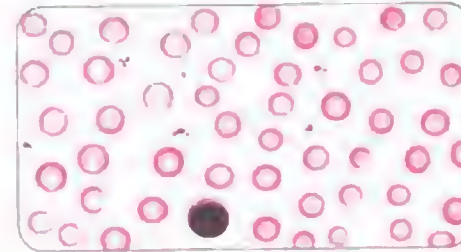
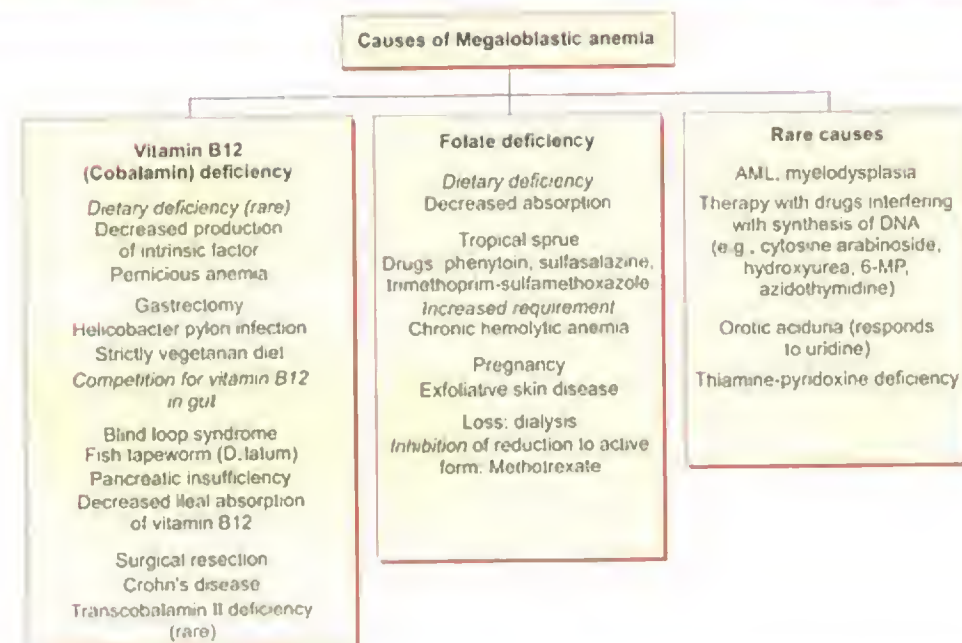


Fig. 11.4: Peripheral blood smear in iron deficiency anemia. Compare the size of red cells with the nucleus of a small lymphocyte.

MEGALOBLASTIC ANEMIA



Clinical Features

- **Vitamin B12 (Cobalamin) deficiency:**
 - A/w **neurologic defects** (paresthesias, gait disturbance, optic neuropathy, and mental status changes).
- **Folate deficiency**
 - Folate deficiency is a/w **neural tube defects** and cleft lip/palate in the fetus; hence folic acid

supplementation of **400 microgram (0.4 mg)** daily throughout pregnancy is recommended.

- Prophylactic folic acid in pregnancy has been found to reduce the subsequent incidence of acute lymphoblastic leukemia (ALL) in childhood.

Blood Findings

- **Hypersegmented neutrophils** (> 5 lobed nucleus)

- **Macro-ovalocytes** (earliest findings) (MCV > 100 fL)
- **Hypercellular bone marrow**
- **Reversal of myeloid:erythroid ratio** (normal is 2-3:1)
- **Increased serum LDH**

Treatment

- Treat with **5-15 mg folic acid** daily.
- Treat with **1000 microgram IM** injection of **Vit B12** (cobalamin) **once every 3 months.**

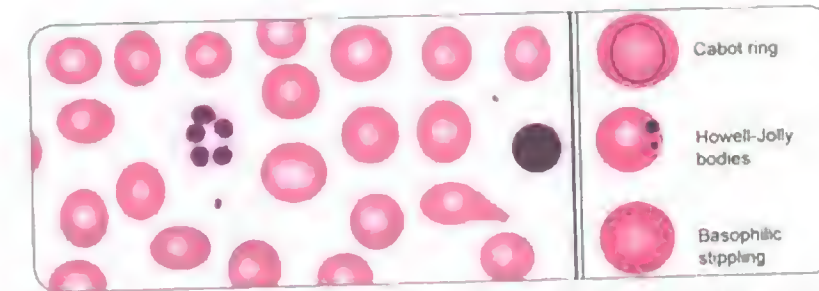


Fig. 11.5: Peripheral blood in megaloblastic anemia showing oval macrocytes, and a hypersegmented neutrophil. A small lymphocyte is shown for comparison of size with red cells. Panel on right shows some morphological abnormalities seen in severe megaloblastic anemia.

Pernicious Anemia

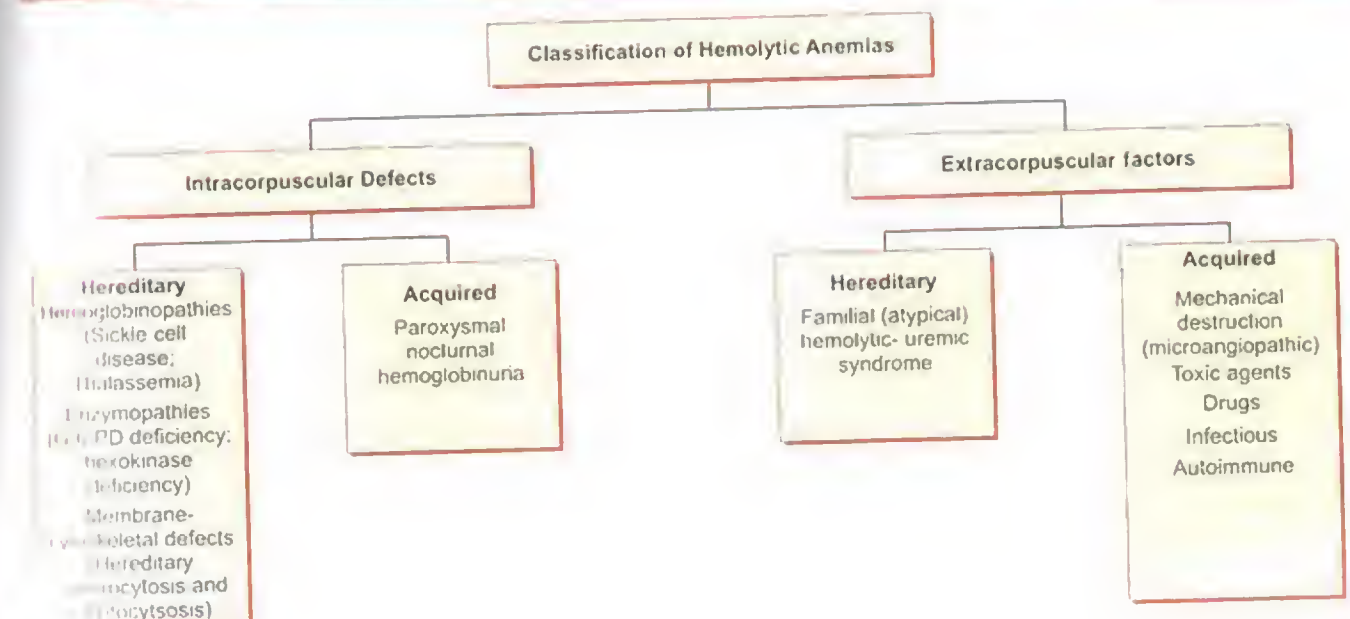
- Due to deficiency of **intrinsic factor of Castle** which is required for absorption of **vitamin B12** from small intestine (**Ileum** is major site of absorption of B12); thus B12 deficiency causes **megaloblastic anemia.**
- **Clinical features**
 - Atrophic glossitis with beefy red tongue
 - Intestinalization of stomach (fundic gland atrophy)
 - Subacute combined degeneration of spinal cord.
- **Schilling test** is used to find out the cause of vitamin B12 deficiency-whether **pernicious anemia** or **malabsorption.**

- **False positive Schilling test** can occur in **renal insufficiency.**

ANEMIA OF CHRONIC INFLAMMATION

- A.k.a **anemia of chronic disease.**
- **Serum ferritin** is most distinguishing feature; it is **↑ 3 times** over basal levels.
- The anemia is typically **normocytic and normochromic**; BUT microcytic, hypochromic anemia may also be seen (esp. in chronic RA or TB).
- **Labs:** ↓ serum iron, ↑ red cell protoporphyrin, a hypoproliferative marrow, transferrin saturation in the range of 15-20%, and a ↑ serum ferritin.

HEMOLYTIC ANEMIAS



Features common to all hemolytic anemias

- **Erythroid marrow hyperplasia:** increased number of erythroid precursors (normoblasts) due to stimulation by erythropoietin
- **Reticulocytosis**
- **Hemosiderin** accumulation in the spleen, liver and bone marrow
- Chronic hemolysis causes elevated bilirubin excretion → **pigment gallstones**.

Sickle Cell Disease

- **Autosomal recessive (AR)** disease.
- **Point mutation** in the β -globin chain of Hb (**glutamic acid replaced by valine at position 6**) leads to the production of HbS, a form of Hb that is poorly soluble when deoxygenated.
- **Heterozygotes** are relatively **malaria resistant**.
 - Also know: **Duffy negativity**, **newborns** (high HbF), **thalassemia** and **G-6-PD deficiency** have **high resistance to *P. falciparum***.
- Factors affecting sickling:
 - **Acidosis, hypoxia, and dehydration** → polymerization of HbS → distortion of RBCs into a **sickle shape** that is susceptible to hemolysis and vascular clumping
 - In heterozygotes (only 40% is HbS, 60% is HbA); this **HbA has an inhibitory effect** on the polymerization of HbS.
 - **Polymerization of HbS** occurs only in **deoxygenated state**.
- **Risk factors:** **African or Latin American heritage**
- **Clinically:**
 - Patients may be **asymptomatic between crises** or may note **bone pain**
 - The main pathogenetic factor is **vaso-occlusive crises**.
 - Stressful events (e.g. infection, illness, trauma) incite sickle cell crises characterized by **severe bone pain, chest pain, "hand foot syndrome" (dactylitis), dyspnea, and priapism**.
 - Physical examination: decreased growth velocity, jaundice or pallor, **splenomegaly (in early stages)**, cardiomegaly, fever, possible leg ulcers.
- **Tests:**
 - ↓ Hb and ↑ reticulocytes; ↑ WBCs (**leukocytosis**)
 - ↓ serum haptoglobin; ↑ indirect bilirubin
 - No HbA, ↑ HbF, and presence of HbS (normally not present) on electrophoresis

- Hb electrophoresis shows **two bands in heterozygous state** (40% HbS and 60% HbA) whereas only **one band in homozygous state**. **HbS is slower** than HbA in moving towards **positive electrode**
- ESR is decreased
- Solubility tests (e.g. SICKLEDEX, Streck, Omal, Nebraska) can detect Hb abnormalities but cannot differentiate between the carrier trait and homozygous disease states
- Blood smear shows **target cells, sickle cells, and nucleated RBCs**.

X-ray changes in sickle cell disease

- **"Fish-mouth" vertebrae** OR **"H shaped" vertebrae**
- **Bone infarction = avascular necrosis** of bony regions with a tenuous blood supply (e.g. femoral head)
- **Periosteal reaction ("bone within bone")**
- **Hair on end** (crew haircut) appearance of skull (also seen in **thalassemia** (classically), **hereditary spherocytosis** and **G6PD deficiency**)



Fig. 11.6: Blood smear in sickle-cell anemia

- **Treatment:**
 - Sickle cell crises are treated with hydration, supplemental oxygen, and narcotic pain control
 - **Transfusions, exchange transfusions, and hydroxyurea** (to shorten crises or to decrease the number of crises)
 - **Bone marrow transplantation** - currently reserved for patients with severe disease and multiple complications
 - Depot medroxy progesterone acetate (DMPA) **prevents sickling** and is the **best contraceptive** for women with sickle cell anemia.
- **Complications**
 - Chronic anemia, pulmonary HTN, heart failure due to cardiac stresses, vascular insufficiency, renal failure, and infections; **Salmonella osteomyelitis** (Salmonella is MC cause of osteomyelitis in sickle cell disease)
 - An **aplastic crisis** may follow **parvovirus B19** infection

- **Aplastic and Sequestration crisis** may occur during **anesthesia**
- **Acute chest syndrome** is severe chest pain due to pneumonia, embolization, or pulmonary infarction and requires pain control and respiratory support
- **Autosplenectomy**, stroke, osteonecrosis of the femoral or humeral head, and multiorgan ischemia may result from vascular occlusion
- Increased risk of infection by encapsulated organisms (e.g. Streptococcus pneumoniae, Hemophilus influenzae, Neisseria meningitidis, Klebsiella) - keep **pneumococcal vaccination up-to-date**.
- **Renal papillary necrosis (Focal Segmental Glomerulosclerosis)** occurs.

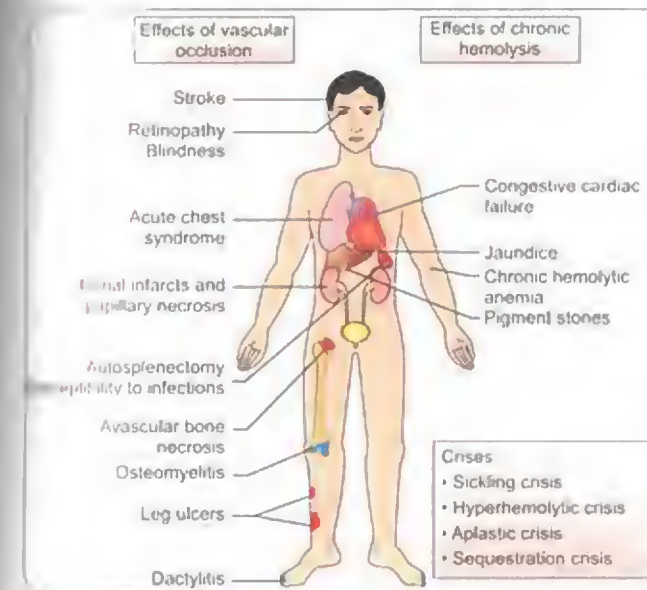


Fig. 11.7: Various effects of vascular occlusion and hemolysis in sickle cell anemia

α -THALASSEMIA

- There are 4- α -globin chains. In α thalassemias the α globin chains is **underproduced**. There is no compensatory increase in any of the other chains.
- α **thalassemia trait** resembles beta thalassemia minor and is asymptomatic.
- α **thalassemia-2 trait**, in which **one** of the four α -globin gene loci is **deleted (gene deletion)**.
- α **thalassemia-1 trait**, with **two** deleted gene loci;
- **HbH disease**, with **three** gene loci deleted; and
- **Hydrops fetalis** with **Hb Barts**, with **all four** gene loci deleted (lethal in utero without transfusion).

β -THALASSEMIA

- In β -thalassemia **minor** (heterozygote) the β chain is **underproduced**.
- In β -thalassemia **major** (homozygote), the β chain is **absent**.
- α chain is **not** affected

β -Thalassemia Minor

- More common than β . thalassemia major.
- Usually asymptomatic.
- **Elevated HbA2** (> 3.5%).
- **Hypochromia** and **microcytosis**; Anemia is minimal

β -Thalassemia Major (Cooley's anemia)

- A/w **markedly increased HbF**.
- **Hypochromia** and **microcytosis** occurs.
- Severe hemolytic anemia due to the abnormal hemoglobins occurs >> resulting profound anemia stimulates erythropoietin release and compensatory erythroid hyperplasia, but the marrow response is sabotaged by the ineffective erythropoiesis. Anemia persists. Erythroid hyperplasia can become exuberant and produce masses of extramedullary erythropoietic tissue in the liver and spleen (**hepatosplenomegaly**).
- Massive bone marrow expansion occurs >> children develop characteristic **"chipmunk" facies**, thinning and **pathologic fracture** of long bones and vertebrae may occur.
- Hemolytic anemia causes hepatosplenomegaly, leg ulcers, gallstones, and **high-output congestive heart failure**.
- **Chronic transfusions with RBCs** improve oxygen delivery, suppress the excessive ineffective erythropoiesis, and prolong life, but the inevitable side effects, notably iron overload, often prove fatal by age 30 years.
- **Cardiac failure** due to secondary **hemochromatosis** can occur.
- **"Crew cut/hair on end"** appearance on skull X-ray and skeletal deformities.
- In **India**, **thalassemia** is MC in **Lohana** and **Sindhi** community of Gujarat.
- In the world, it is common in Mediterranean, parts of Africa and South East Asia.
- **Iron chelating drugs** used include: **desferrioxamine; deferiprone; deferasirox**.
- **Children with Thalassemia and Iron overload** are at an increased risk for infection with **Yersinia enterocolitica**

- **Apt test:** Qualitative test for HbF
- **Kleihauer betke test:** Quantitative test for HbF
- **Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT)** — rapid screening tests for mass screening of β -thalassaemia trait.
- APT test and Kleihauer test are described in a detailed table in **pediatrics chapter** (Pg 665).

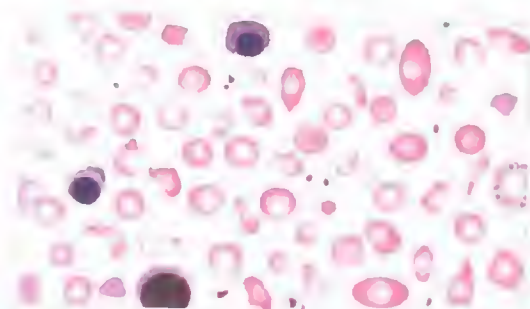


Fig. 11.8: Blood smear in thalassemia major showing microcytic hypochromic red cells, nucleated red cells, anisopoikilocytosis, target cells, basophilic stippling, and polychromasia

G6PD Deficiency

- Maintenance of integrity of RBC membrane is as follows:
 - **HMP pathway** — Production of NADPH, which maintains glutathione in reduced state — this in turn detoxifies free radicals and peroxides.
 - **Glycolysis** — to produce 2ATP, which maintains Na^+ and K^+ distribution across the cell membrane.
- **BUT In G6PD deficiency** → ↓ NADPH → poor defense against oxidizing agents → RBC lysis → hemolytic anemia.
- **XLR;** resistant to falciparum malaria.
- G6PD deficiency is more among **Blacks**.
- Primaquine led to the discovery of G6PD deficiency.
- **Precipitating factors in G6PD deficiency**
 - Infection (**MC cause**);
 - Oxidant drugs (*see table*)
 - Favism (ingestion of fava beans).
- **Clinically:**
 - The vast majority are **asymptomatic** throughout their lifetime;
 - However, all of them have an increased risk of developing **neonatal jaundice (NJ)** and a risk of developing **acute hemolytic anemia** when challenged by a number of oxidative agents.
 - NJ — peak incidence of clinical onset is **between day 2 and day 3**.
 - A very small minority of subjects with G6PD deficiency have **chronic nonspherocytic hemolytic anemia (CNSHA)**

Blood Picture

- **Heinz bodies** — altered Hb precipitates within RBCs seen on supravital staining with methyl violet
- **Bite cells (Blister cells)** result from phagocyte removal of Heinz bodies from RBCs.
- **Hemighost cells:** Red cells that appear to have unevenly distributed hemoglobin.
- Drugs with **definite risk of causing hemolysis in G6PD deficiency** is given in below table:

Drug Class	Examples
Antimalarials	Primaquine Dapsone/chlorproguanil
Sulfonamides/sulfones	Sulfamethoxazole others Dapsone
Antibacterial/antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole
Antipyretic/analgesics	Acetanilide Phenazopyridine
Other	Naphthalene Methylene blue Rasburicase

Hereditary Spherocytosis

- Incidence = 1 in 5000. Its identification is credited to **Minkowski and Chauffard**.
- Genetic defect in RBC membranes (**ankyrin (MC) spectrin or actin deficiency**) resulting in → **spherical RBCs** → unable to pass through spleen and get trapped in spleen (**extravascular hemolysis**)
- Clinically: Anemia, moderate splenomegaly, jaundice, pigment gallstone (40-50%)
- **Lab tests**
 - **Spherocytes with Increased MCHC**
 - **Coombs negative**
 - **Osmotic fragility test** (red cells are abnormally susceptible to lysis in hypotonic media)
 - The acid glycerol lysis test,
 - The eosin-5' -maleimide (EMA)-binding test, and
 - SDS-gel electrophoresis of membrane proteins;
 - **Ektacytometry** used to confirm
- **Treatment**
 - **Splenectomy** is the only treatment
 - In **mild cases:** avoid splenectomy
 - In **moderate cases:** delay splenectomy until puberty or
 - In **severe cases:** delay splenectomy until 4-6 years of age
 - **Antipneumococcal vaccination** before splenectomy is compulsory
 - **Howell Jolly bodies** are present after splenectomy.

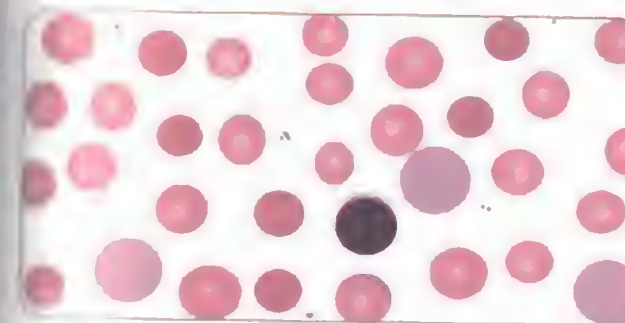


Fig. 11.9: Blood smear in hereditary spherocytosis. Spherocytes are small (compare with small lymphocyte), dense cells with no central pallor. Polychromatic cells are also increased due to hemolysis

Paroxysmal Nocturnal Hemoglobinuria

- Due to mutations in the **PIGA gene** (phosphatidylinositol glycan A gene).
- RBC membrane defect that is **acquired**.
- RBCs have ↑ sensitivity to **complement-mediated lysis** (impaired synthesis of **GPI anchor** in RBC membrane) — **intravascular hemolysis**.
- **Episodic hemoglobinuria** resulting in **reddish brown urine** most often in the **first morning urine**.
 - Prone to **anemia** and **large vessel thrombosis**, especially mesenteric, portal and hepatic vein thromboses — **MC cause of death**.
 - As this is a monoclonal stem cell disorder, **PNH may progress either to aplastic anemia, to myelodysplasia, or to AML**.
 - ↑ urine **hemosiderin**.
 - **Best screening test** is **flow cytometry** to demonstrate **deficiency of CD59 and CD55** (decay accelerating factor) on RBCs.
 - Old screening tests: **Ham's test** (acidified serum test—highly reliable but done in only few labs), **Sucrose hemolysis test** — **unreliable**; **sugar water test**.
 - Treatment: Iron replacement, folic acid supplementation, prednisolone, **anti-complement C5 antibody eculizumab**.

Triad of PNH

- Intravascular hemolysis
- Pancytopenia
- Tendency for venous thrombosis

Microangiopathic Hemolytic Anemia

- Results from **mechanical damage to RBCs** as they pass through very small orifices or damaged and sclerosed vessels—i.e. traumatic intravascular hemolysis. **Schistocytes/helmet cells** seen on blood smear.

- Causes are **HUS, TTP, DIC, SLE, HIV, PAN, malignant HTN (eclampsia), ARF, prosthetic heart valves, necrotizing enterocolitis**
- **Zieve's syndrome:** during withdrawal from **prolonged alcohol abuse**; defined by **hemolytic anemia, hyperlipoproteinemia** (excessive blood lipoprotein), **jaundice**, and **abdominal pain**.

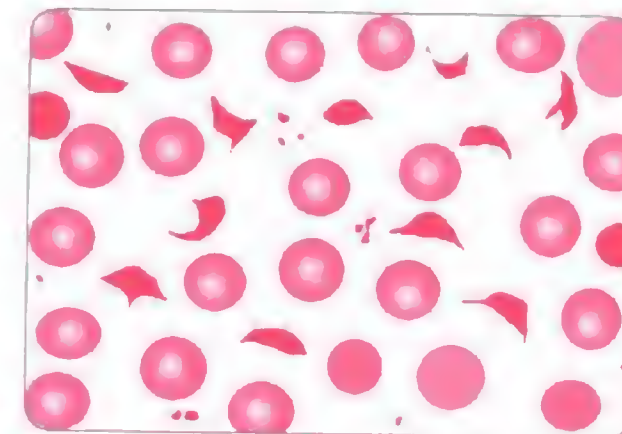
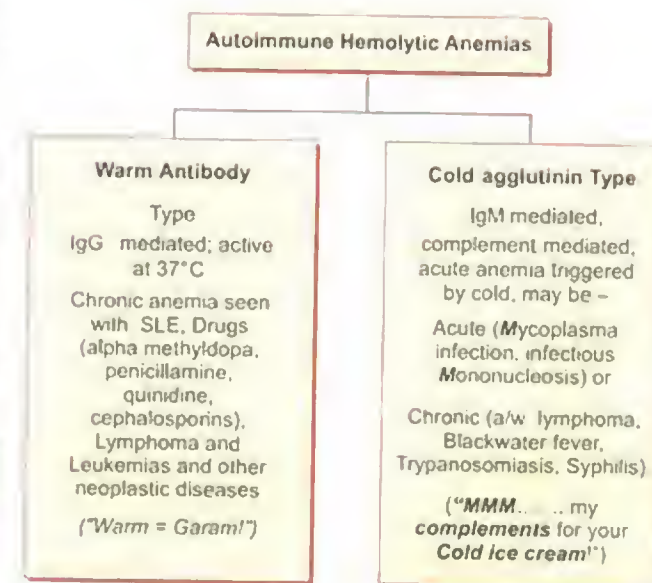


Fig. 11.10: Blood smear in microangiopathic hemolytic anemia showing many fragmented cells (schistocytes)



APLASTIC ANEMIA

- **Pancytopenia** caused by failure or destruction of multipotent myeloid stem cells, with inadequate production of differentiated cell lines.
- Etiology: *See table further.*

Secondary	Inherited
<ul style="list-style-type: none"> Radiation Drugs and Chemicals: benzene, chloramphenicol, alkylating agents, antimetabolites, Viruses (Parvovirus B19, EBV, HIV, Hepatitis A/E) Immune diseases (Eosinophilic fasciitis, Hyper-immunoglobulinemia, Large granular lymphocytosis, Thymoma/thymic carcinoma, Graft-versus-host disease in immunodeficiency) Paroxysmal nocturnal hemoglobinuria Pregnancy Idiopathic 	<ul style="list-style-type: none"> Fanconi anemia Dyskeratosis congenita Shwachman-Diamond syndrome Reticular dysgenesis Amegakaryocytic thrombocytopenia Familial aplastic anemias Preleukemia (monosomy 7, etc.) Nonhematologic syndrome (Down, Dubowitz, Seckel)

- Symptoms: Fatigue, malaise, pallor, purpura, petechia, mucosal bleeding, infections.
- Pathology: Severe anemia, neutropenia and thrombocytopenia with normal cell morphology; **hypocellular bone marrow** with **fatty infiltration**. Diagnose with **bone marrow biopsy**.
- Bone marrow aspiration yields 'dry tap.'
- Treatment: Withdrawal of offending agent:
 - **Allogenic bone marrow transplantation: Best therapy** for the younger patient with a fully histocompatible sibling donor.
 - Mild cases: **RBCs and platelet transfusion**, erythrocyte growth factors (**epoetin** or **darbepoetin**); myeloid growth factors (**filgrastim** G-CSF; or **Sargramostim** GM-CSF).
 - Severe cases: Immunosuppression with **Antithymocyte globulin (ATG)** and **cyclosporine**.

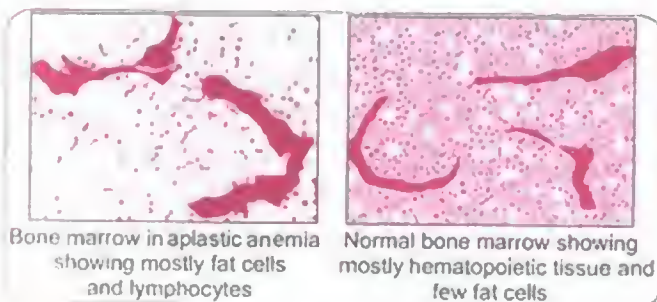


Fig. 11.11: Bone marrow cellularity, comparison of normal and aplastic bone marrow

EXTRA EDGE

- Fanconi anemia: AR, aplastic anemia, hypoplasia of kidneys and spleen; radius and thumb anomalies.
- Shwachman-Diamond syndrome**, presentation is early in life with **neutropenia** with **pancreatic insufficiency** and **malabsorption**; etiology is mutations that may affect liver, ribosomal biogenesis AND marrow stroma function.
- Dyskeratosis congenita** is characterized by the triad of **mucous membrane leukoplakia**, **dysplastic nails**, **reticular hyperpigmentation**, and with the development of **aplastic anemia** in childhood.

Pure Red Cell Aplasia (PRCA)

- Only **erythroid** precursors are suppressed in bone marrow.
- Acute PRCA** caused by **Parvovirus B19** infection.
- Chronic PRCA** caused by **thymoma** or **autoimmune phenomenon**.
- Diamond-Blackfan anemia**, or congenital PRCA is diagnosed at birth or in early childhood and often responds to **glucocorticoid** treatment; etiology is **mutations in ribosome protein genes**.

Myelophthisic Anemia

- A form of bone marrow failure where **space-occupying lesions** replace normal marrow elements.
- MC** cause is **metastases** to marrow (from breast, lung or prostate).
- It is a/w **leukoerythroblastic** blood picture (see topic below).

Leukoerythroblastic Blood Picture

- This means that **primitive red cells** (nucleated RBCs or erythroblasts) **are present, together with primitive white blood cells** (myelocytes) in peripheral blood.
- This usually (but not always) **indicates that the bone marrow has been infiltrated or replaced by secondary cancer or fibrosis**.

Leukoerythroblastic blood picture seen in

- Secondary Ca of Bone (**MC** cause)
- Myelofibrosis
- Marble bone disease (Osteopetrosis)
- Severe hemolytic anemia in infants - Erythroblastosis fetalis
- Thalassemia major, especially after splenectomy
- Multiple myeloma, Lymphoma
- Gaucher's; Niemann-Pick disease

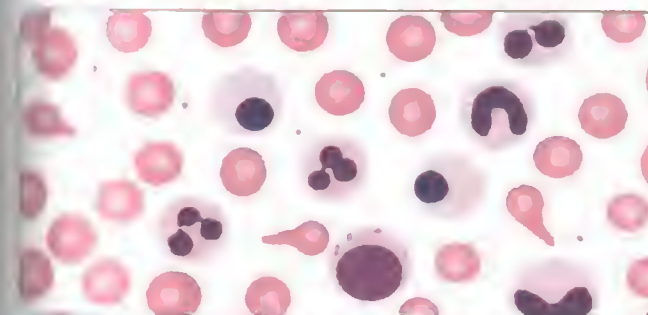


Fig. 11.12: Leukoerythroblastic blood picture showing immature white and red blood cells in peripheral blood. Teardrop red cells are also present.

Neutrophil (Leukocyte) Alkaline Phosphatase (LAP)

Low values	High values
CML - Chronic myeloid leukemia	Polycythemia vera
PNH - paroxysmal nocturnal hemoglobinuria	Leukemoid reaction
ITP - idiopathic thrombocytopenic purpura	Drugs (steroids, OCPs)
IM - Infectious mononucleosis	Myelofibrosis
Refractory anemias - sideroblastic, sickle cell, pernicious, aplastic	Pregnancy
Hypophosphatemia	MI
	Down's syndrome
	Diabetic acidosis
	Multiple myeloma, Hodgkin's disease, Hairy cell leukemia

MYELOPROLIFERATIVE DISORDERS

WHO Classification of Chronic Myeloproliferative disorders

- Chronic myeloid leukemia, BCR-ABL-positive
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia, not otherwise specified
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocytosis
- Mastocytosis
- Myeloproliferative neoplasms, unclassifiable

Polycythemia

- True erythrocytosis**, with an **elevated RBC mass**, is distinguished from **spurious erythrocytosis** caused by a constricted plasma volume.
- Primary polycythemia (polycythemia vera)** is a **bone marrow disorder** characterized by autonomous over-

production of erythroid cells. Erythroid production is **independent of erythropoietin**, and the **serum erythropoietin level is low**.

- Causes of polycythemia:
 - Spurious polycythemia
 - Secondary polycythemia
 - Hypoxia: Cardiac disease, pulmonary disease, high altitude
 - Carboxyhemoglobin: Smoking
 - Renal lesions
 - Erythropoietin-secreting tumors (rare)
 - Polycythemia vera.
- JAK2V617F** mutation; **Splenomegaly**; **pruritus** (after warm bath); **thrombosis**
- ↑ RBC mass; ↑ hematocrit (> 50%); ↑ WBC and ↑ platelet count; **NORMAL** arterial oxygen saturation.
- The treatment of choice is **serial phlebotomy**; one unit of blood (approximately 500 mL) is removed weekly until the hematocrit is less than 45%; **hydroxyurea**; **Anagrelide** in refractory patients. **Daily aspirin** should be given.

Myelofibrosis

- Presents in the **same way as hairy cell leukemia** (**pancytopenia** and **marked splenomegaly**).
- Teardrop poikilocytosis** on peripheral smear.
- Leukoerythroblastic** blood picture, giant abnormal platelets (**megakaryocytes**).
- No specific treatment.

Essential Thrombocytosis

- Markedly elevated platelet count**.
- Erythromelalgia** - headache, visual disturbances, pain in the hands.
- MC cause of death is **thrombosis**, bleeding also may occur.
- Absence** of BCR/ABL gene (Philadelphia chromosome)
- Treatment: **Hydroxyurea** to lower platelet count; anagrelide may be used but not so effective; give daily aspirin.

Laboratory features of myeloproliferative syndromes

	White Count	Hematocrit	Platelet Count	Red Cell Morphology
Chronic myeloid leukemia	↑↑	N	N or ↑	N
Myelofibrosis	↓ or N or ↑	↓	↓ or N or ↑	Abnormal

Child

	White Count	Hemato- crit	Platelet Count	Red Cell Morphol- ogy
Polycythemia vera	N or ↑	↑	N or ↑	N
Essential thrombocytosis	N or ↑	N	↑↑	N

Myelodysplastic Syndrome

- Presents in elderly patients with **pancytopenia**, **elevated MCV**, **low reticulocyte counts** and **macro-ovalocytes**.
- Special **bilobed neutrophil** called "**Pelger Huet**" cell is present.

- "**Pawn ball megakaryocytes**": a megakaryocyte with single nuclear lobe or multiple separate nuclei.
- "**Dohle bodies**": aggregates of **rough endoplasmic reticulum** in **neutrophils**.
- Small number of blasts are present – mild slow progressive **preleukemia syndrome**.
- **Myelodysplasia may progress to AML**.
- Most patients die with bleeding.
- Supportive treatment with multiple transfusions needed.
- **MC cytogenetic abnormality** in MDS is 5q- (5q deletion) syndrome. (See Fig. 11.13)
- **Lenalidomide** is accepted standard treatment for 5q MDS.

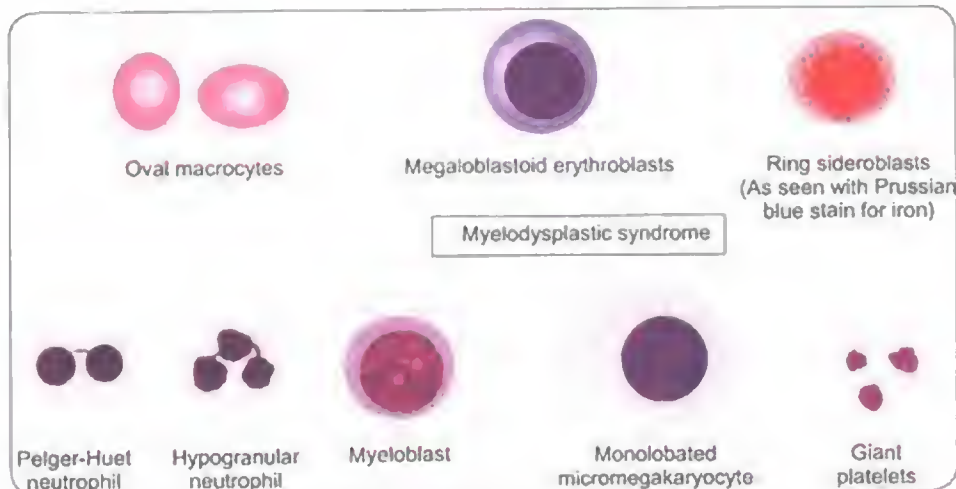


Fig. 11.13: Some characteristic morphological abnormalities in MDS

EXTRA EDGE

Hereditary Neutrophil disorders with abnormal morphology:

- **Pelger huet** anomaly: Normal neutrophil function; special **bilobed neutrophil**; due to mutation in lamin-beta receptor (autosomal dominant)
- **May Hegglin** anomaly: **Giant platelets**, thrombocytopenia, and large **blue cytoplasmic inclusions** resembling giant Dohle bodies present in eosinophils, neutrophils, basophils and monocytes. (autosomal dominant)
- **Alder Reilly** anomaly: Associated with genetic **mucopolysaccharide** disorders. Intense **azurophilic granulation** of neutrophil cytoplasm. (autosomal recessive)
- **Myelokathexis**: Neutrophils show **hypersegmentation**, **pyknotic** nuclei and cytoplasmic **vacuoles**.

LEUKEMIAS

Chromosomal Translocations in Leukemias and Lymphomas

Translocation	Associated disorder
t(9;22)	CML (Philadelphia chromosome)
t(15;17)	AML M3
t(8;14)	Burkitt's lymphoma (c-myc activation)
t(14;18)	Follicular lymphoma (bcl-2 activation)
t(11;14)	Mantle cell lymphoma
t(11;22)	Ewing's sarcoma
t(8;21)	AML M2
t(11;18)	MALT lymphoma

Viruses associated with Lymphoid Malignancies

EBV	Burkitt's lymphoma Post-organ transplant lymphoma Primary CNS diffuse large B-cell lymphoma Hodgkin's lymphoma Extranodal NK/T-cell lymphoma, nasal type
HTLV I	Adult T-cell leukemia/lymphoma
HTLV	Diffuse large B-cell lymphoma Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
HHV 8	Primary effusion lymphoma Multicentric Castleman's disease

CHRONIC MYELOID LEUKEMIA (CML)

- Malignancy of **myeloid cells**. Occurs most often in **middle aged adults**; **a/w ionizing radiation** and **benzene exposure**; **cigarette smoking** accelerates the progression to blast crisis
- It is often stable for several years (**chronic phase**) and then accelerates into AML (**blast crisis**).

Philadelphia chromosome

- t(9;22) (q34;q11.2) - found in **90%** of cases
- **bcr-abl fusion gene** (this gene is **best test for CML**).
- It persists during remission, and the **prognosis is worse if absent**.
- Also reported to occur in **myelofibrosis** and **polycythemia rubra vera**.

- **Symptoms** are chronic and insidious, weight loss, tiredness, gout, **priapism**, abdominal pain.
- **Signs**: **massive splenomegaly**, variable hepatomegaly, anemia, sternal tenderness, bruising esp. during blast crisis, painless lymphadenopathy.

• **Tests**:

- WBC ↑↑↑ (leukocytosis with mainly neutrophils and basophils); WBC > 1 lakh cells/mm³
- **Leukocyte alkaline phosphatase (LAP) decreased** (In leukemoid reaction, LAP is normal or increased!);
- **Myeloid hyperplasia** with **left shifted** maturation (i.e. Myeloid:Erythroid ratio = **10:1** with increased myelocytes and metamyelocytes)
- Bone marrow is hypercellular; "**sea-blue histiocyte** (**pseudo-Gaucher cells**)" - macrophage with wrinkled, green blue cytoplasm may be seen.

• **Treatment**:

- **Drug of choice**: **BCR-ABL tyrosine kinase inhibitors**; specifically targets and eliminates the CML clone - leads to **90% hematological remission**
- I generation = **Imatinib besylate** (Gleevec),
- II generation = **Nilotinib, dasatinib and bosutinib**
- III generation = **Ponatinib** (active against T315I mutation)
- **Allogenic stem cell transplantation** is the **only curative therapy** for CML (when feasible is the treatment of choice)
- **Omacetaxine** (Synribo), a protein synthesis inhibitor with more selective inhibition of the synthesis of the BCR-ABL1 oncoprotein - approved for the treatment of chronic- and accelerated-phase CML after failure of two or more tyrosine kinase inhibitors.

- Three **prognostic scoring systems** exist to predict the **clinical response to tyrosine kinase inhibitors** and outcome:

- **Sokal** score;
- **Hasford** score and
- **EUTOS** (European Treatment and Outcome Study).

Splenomegaly

Causes of "**massively enlarged**" spleen, palpable **more than 8 cm** below the left costal margin or its drained **weight is ≥1000 g**

- Chronic myelogenous leukemia
- Lymphomas
- Chronic lymphocytic leukemia
- Hairy cell leukemia
- Myelofibrosis with myeloid metaplasia
- Gaucher's disease
- Sarcoidosis
- Autoimmune hemolytic anemia
- Polycythemia vera
- Diffuse splenic hemangiomatosis

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- Malignancy of **well-differentiated B lymphocytes**; seen in **older adults** (> 60 years).
- **Clinical features**: often **asymptomatic**, **incidentally lymphocytosis discovered**; **generalized lymphadenopathy** and **hepatosplenomegaly**
- In about 5% of cases, while the systemic disease remains stable, an isolated lymph node will be transformed into an **aggressive large cell lymphoma** (**Richter's syndrome**)

Blood Tests for CLL

- **Absolute lymphocytosis** of small, mature-looking lymphocytes **expressing CD5**.
 - Often normocytic normochromic anemia (**autoimmune hemolysis** - *warm and cold*) may contribute to this.
 - **Thrombocytopenia** from marrow infiltration (rarely antiplatelet antibodies).
 - **Smudge cells / basket cells** on peripheral smear which are ruptured nuclei of lymphocytes - look like **squished jelly donuts**;
 - **Hypogammaglobulinemia** is common
- Two staging systems used are **Rai classification** system and **Binet staging** system.
 - **Treatment:**
 - Asymptomatic - no treatment;
 - For high risk disease: the initial treatment of choice is the combination of the chemotherapeutic agent **fludarabine** + antibody **rituximab**, with or without the addition of the chemotherapeutic drug **cyclophosphamide**. (**chlorambucil** was used before fludarabine).
 - **Steroids and splenectomy** are used for autoimmune hemolysis (avoid fludarabine).
 - **Newer agents:** Alemtuzumab, lenalidomide, flavopiridol.

ACUTE LYMPHOBLASTIC LEUKEMIA

- **MC childhood leukemia** +; About **80%** of cases are of **B-cell origin**. Their nuclei contain the enzyme **TdT**.
- Peak incidence between **3 and 7 years of age**; ↑ incidence in **Down's syndrome**. Age between 2-10 years - **good prognosis**.
- **Immunological classification:**
 - **pre-B ALL (MC, ~75%); Classic childhood ALL**. Often have splenomegaly and **low WBC count** (< 25,000/ μ L). **Good prognosis**.
 - **T-cell ALL**: has a peak in adolescent males, presenting with a **mediastinal mass**, high WBC count, CNS disease.
 - **B-cell ALL**: **rare**, **immunoglobulins** present on blast cells. **Poorest prognosis**.
- Morphological classification: The **FAB system** (French, American, British) divides ALL into 3 types L1, L2, L3 by microscopic appearances.
- **Chromosomal changes**
 - **Hyperploidy** (51-60 chromosomes), fairly common in pre-B cell ALL and has a **good prognosis**.
 - A **Philadelphia chromosome** - **rare**, **t(9;22)** and **t(1;19)** and **t(8;14)** translocations are a/w **poor prognosis**.
 - **t(12;21)** a/w **good prognosis**.

- **Clinical features:** Signs are due to bone marrow failure: anemia, infection, and bleeding. Also: bone pain, arthritis, splenomegaly, lymphadenopathy, thymic enlargement, CNS involvement—e.g. cranial nerve palsies, metabolic abnormalities (as a part of tumour lysis syndrome)—hypo/hyperkalemia.
- **Tests:**
 - **Tdt** is present in **95% cases of ALL**;
 - **CALLA** - Common **ALL** Antigen, (**CD10**) positive;
 - **platelets** are ↓↓;
 - ↑ **LDH** and **uric acid**.
- **Treatment:** **Nearly all children achieve complete remission** and **80%** achieve long-term leukemia free survival. Phases of treatment and their objectives are as below:
 - **Induction therapy:** **To induce remission (i.e., to destroy all blasts)**. Combination chemotherapy. **Adults:** Vincristine, prednisone, daunorubicin, asparaginase. **Children:** Vincristine, prednisone with or without asparaginase.
 - **Consolidation:** **To kill any residual leukemia**. Multi-agent alternating chemotherapy. CNS prophylaxis with **intrathecal methotrexate** with or without whole brain radiation. Allogeneic bone marrow transplant for young adults or high-risk disease or second remission.
 - **Maintenance therapy:** **to maintain remission**, daily **methotrexate**, or **6-MP** or both.
 - Prevent infections with antibiotics.

EXTRA EDGE

- TdT is expressed in malignant tumors of lymphoblastic lineage (including **precursor-B and T lymphoblastic leukemia/lymphoma** and lymphoid blast crisis of chronic myeloid leukemia) and in a subset of acute myeloid leukemias.
- **Inotuzumab ozogomicin** and **Tisagenlecleucel** are new FDA approved drug for the treatment of adults with relapsed or refractory B-cell precursor ALL.

Favorable prognosis in ALL

- Age between 2 and 10 years
- Low WBC count
- Hyperploidy
- Trisomy of chromosomes 4,7,10
- Presence of **t(12;21)**

Poor prognosis in ALL

- Age < 2 years
- Presentation in adolescence or adulthood
- Translocation involving MLL gene
- Peripheral blast count > 1 lakh

ACUTE MYELOID LEUKEMIA (AML)

- Chiefly an **adult disease with a median age at presentation of 50 years** and increasing incidence with each decade of advancing age.

Etiology

- **Hereditly:** **Down's syndrome**; defective DNA repair (**Fanconi anemia**, **Bloom syndrome**, and **ataxia-telangiectasia**), congenital neutropenia (**Kostmann syndrome**)
- **Ionizing radiation**
- **Chemicals:** exposure to **benzene**, **cigarette smoke**, **petroleum products**, **paint**, **embalming fluids**, **ethylene oxide**, **herbicides**, and **pesticides**.
- **Anticancer drugs** are the leading cause of **therapy-associated AML**:
 - **Alkylating agent**-associated AML occur **4-6 years** after exposure, with aberrations in **chromosomes 5 and 7**.
 - **Topoisomerase II inhibitor**-associated AML occur **1-3 years** after exposure, with aberrations involving **chromosome 11q23**.

Classifications

- A major difference between the WHO and the FAB systems is the **percentage of blast cells** for a diagnosis of AML; it is **20% in the WHO** classification and **30% in the FAB**. ("More the merrier"! Hence **30** is **FABulous**!)

Revised FAB Classification of AML

M0 Minimally differentiated AML	Immature morphology
M1 AML without differentiation	
M2 AML with maturation	t(8;21) - favorable prognosis , chloromas ; MC type
M3 Acute Promyelocytic leukemia (APML)	Patients are younger; Multiple Auer rods within myeloblasts (peroxidase + cytoplasmic inclusions), t(15;17) is characteristic; excellent response to tretinoin; treatment can release Auer rods → often develop DIC
M4 Acute myelomonocytic leukemia	inv (16), good prognosis, lymphadenopathy , CNS involvement
M5 Acute Monocytic leukemia	Stomatitis , gingival hypertrophy , rectal fissures , Nonspecific esterase +
M6 Acute erythroleukemia	Di Guglielmo's disease , bizarre multinucleated erythroblasts
M7 Acute megakaryocytic leukemia	Megakaryoblasts > 30% of all nucleated cells; myelofibrosis; a/w Down's syndrome

WHO classification of AML

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related AML
- AML, not otherwise specified

EXTRA EDGE

- Most **definitive** sign of myeloid differentiation: **Auer rods**.
- Cluster of Auer rods are known as **faggot**.
- Molecular markers with a **favorable prognosis** in AML:
 - NPM1 mutations
 - CEBPA mutations
 - MLL-181a-overexpression.
- Occasionally blast cells are entirely absent from the blood—'aleukemic leukemia'.
- AML with **t(15;17)** has best prognosis.

Treatment

- **Induction:** Combination chemotherapy with cytarabine and an anthracycline (daunorubicin, idarubicin)
- **Tretinoin** with idarubicin for **APML**, **M3**; **APML with relapse** - **arsenic trioxide**.
- **Consolidation:** High dose cytarabine.
- Autologous or allogeneic BMT for high-risk disease or second remission.

New Drugs for AML in 2017

- **Midostaurin** is a multiple protein kinase inhibitor (including FLT3 and KIT) that has FDA approval for **FLT3 positive AML**. It is also approved for **systemic mastocytosis**. AML a/w **FLT3 mutation** has **poor prognosis** due to higher relapse rate.
- **Enosidenib** is FDA approved for treating IDH2 mutation positive AML.

HAIRY CELL LEUKEMIA

- **Mature B lymphocytes** in **Middle aged (55 years) Men** (M:F = 5:1).
- **Massive splenomegaly** is present. ("Mature Middle aged Men will B Massively Hairy").
- Patients present with fatigue and frequent infections; **lymphadenopathy** is **RARE** ("rare in hairy!")
- **Pancytopenia** is the hallmark; **leukemic cells with hairy cytoplasmic projections** are present in blood smear and bone marrow biopsy.
- Bone marrow is usually **infiltrable**, (**dry tap**).
- Hairy cells stain with tartrate resistant acid phosphatase (**TRAP**).
- The tumor cells have strong expression of **CD22**, **CD25**, and **CD103**; soluble **CD25** level in serum is an **excellent tumor marker** for disease activity.

- Pan B cell marker is **CD19**.
- MC a/w **serine/threonine kinase BRAF** mutation.
- The treatment of choice is **cladribine** (2 chlorodeoxyadenosine, 2-CDA).
- Treatment with **pentostatin** is somewhat similar but this drug is *more cumbersome to administer*.
- Chemotherapy resistant patients have responded to **venetoclax**.

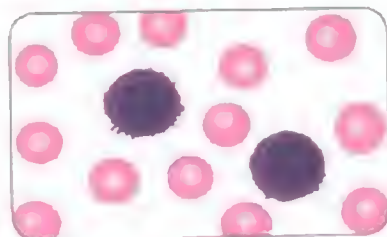


Fig. 11.14: Blood smear in hairy cell leukemia

LYMPHOMAS

Differences between Hodgkin's and Non-Hodgkin's Lymphoma

Hodgkin's	Non-Hodgkin's
More commonly localized to a single axial group of lymph nodes (e.g. cervical; mediastinal; para-aortic)	More common involvement of multiple peripheral nodes

Contd...

Contd...

Hodgkin's	Non-Hodgkin's
Orderly spread by contiguity	Noncontinuous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal presentation rare	Extranodal presentation common

Hodgkin's Lymphoma — Clinical

- Presence of **Reed-Sternberg cells** (RS cells are **CD30+** and **CD15+**, express **PAX5**, B cell origin, giant cell with binucleated/bilobed - 'owl eyes', 45 microns diameter)
- Localized **single group** of nodes - presents at **cervical nodes**; extranodal rare
- Spreads **centrifugally** away from the center
- **Constitutional** ("B") features—low grade fever (**Pel-Ebstein fever**), weight loss, night sweats - implies widespread disease
- **Mediastinal adenopathy**
- 50% cases a/w EBV; **bimodal distribution** - young and old
- Two important paraneoplastic syndromes seen in Hodgkin's lymphoma are: secondary amyloidosis (AA type) and alcohol induced pain in lymph nodes.
- Treatment: **Radiotherapy and chemotherapy**.

Contd...

Hodgkin's Lymphoma Types

Type	Morphology	Clinical Features	Prognosis
Classic Hodgkin's lymphoma			
Nodular sclerosing (70%);	Frequent Lacunar cells and occasional RS cells Collagen banding seen (collagen separates nodular areas) CD15+ and CD30+; EBV rare	MC subtype; M=F ; Affects mainly young adults Usually stage I or stage II disease Frequent mediastinal adenopathy	Excellent
Mixed cellularity (25%)	Numerous RS cells MC a/w EBV (70%)	More than 50% present as stage III or IV disease; Affects M > F . Biphasic incidence—peaking in young adults and again in those > 55 years MC subtype in developing countries More commonly a/w type B symptoms	Intermediate
Lymphocyte rich (5%)	Frequent mononuclear and RS cells seen	Older males affected; M > F	Excellent
Lymphocyte depleted (rare)	Reticular variant ; bizarre RS cells seen (mummified or pleomorphic RS cells); Hodgkins cells (atypical histiocytes) seen in this variant	Rarest subtype More common older males and HIV positive people Often presents with disseminated disease	Poorest

Type	Morphology	Clinical Features	Prognosis
Nodular Lymphocyte predominant Hodgkin's lymphoma (Nonclassic)			
Lymphocyte predominant	Frequent Papern cells (L and H cells - Lymphohistiocytic cells) in background of follicular dendritic cells and reactive B cells RS cells are rare NO a/w EBV; NO CD15 or CD30 BUT CD20+ and CD45+	Young males , cervical or axillary lymphadenopathy	Excellent - Best

EXTRA EDGE

- Classical **R-S cells** are **CD15 and CD30 +ve** (CD45 and CD 20 negative).
- **L and H cells** are **CD20 and CD45 +ve** (CD15 and CD30 negative).

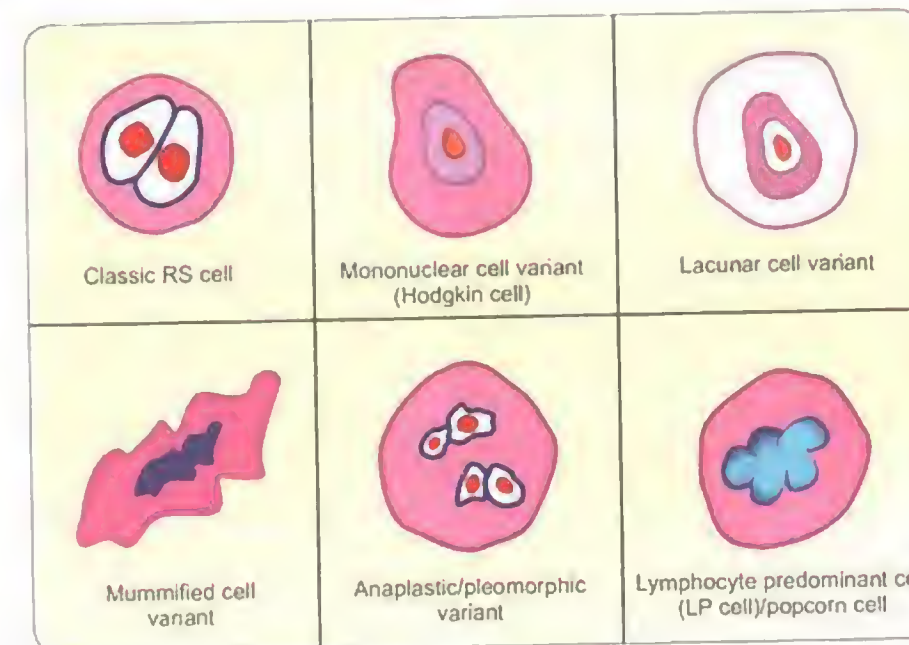


Fig. 11.15: Diagrammatic appearances of Reed-Sternberg cells and its variants

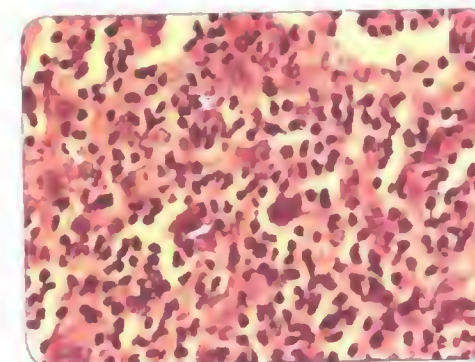


Fig. 11.16: Microscopic appearance of Hodgkin lymphoma showing RS cells (short arrow and inset) and Hodgkin cells (long arrow) within the background of mixed population of reactive cells

EXTRA EDGE

- Activation of the transcription factor **NF-κB** is a common event in classical Hodgkin's lymphoma.

Non-Hodgkin's Lymphoma Types (NHL)

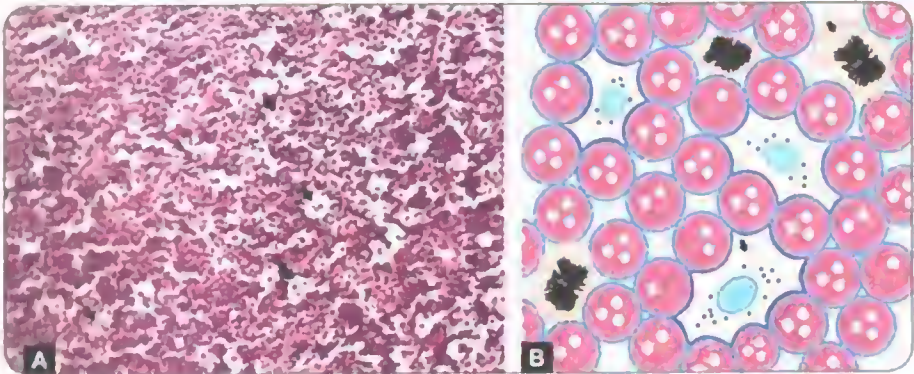
- A/w infections: **EBV** - Burkitt's lymphoma; **HIV** - CNS lymphoma; **HTLV** - T cell lymphoma; **H. pylori** - gastric MALToma
- Presents with **widespread disease**. Multiple peripheral nodes; extranodal involvement common; **noncontiguous** spread
- Majority involve **B cells** (NHL T cell lymphomas involve skin as **Mycosis fungoides** and **Sézary syndrome**)

- NO hypergammaglobulinemia
- Few "B" features

- Peak at 20-40 years
- Serum LDH is prognostic marker.

NHL Types

Type	Comments
Small lymphocytic lymphoma	Seen in adults; B cell type; like CLL with focal mass, low grade
Follicular lymphoma (small cleaved)	Seen in adults; B cell type; t(14;18); anti-apoptotic BCL-2 overexpression; difficult to cure, indolent course
Diffuse large B cell lymphoma	80% adults, 20% children; 80%; localized disease with GIT and brain (a/w HIV)
Mantle cell lymphoma	Seen in adults; B cell type; t(11;14); poor prognosis, CD5+; overexpression of cyclin D1 SOX11 is positive in cyclin D1 negative cases
Lymphoblastic lymphoma	Most often children, immature T cell type; commonly presents with ALL and mediastinal mass; very aggressive
Burkitt's lymphoma	Most often children, MC in males; a/w EBV B cell type; t(8;14) c-myc gene moves next to heavy chain Ig gene; 'starry sky' appearance (sheets of lymphocytes with interspersed macrophages); Jaw lesion in endemic form in Africa; pelvis or abdominal mass in sporadic form.



Figs 11.17A and B: Burkitt lymphoma composed of medium-sized lymphoid cells admixed with benign macrophages (narrow arrow) giving a "starry sky" appearance. Numerous mitotic figures are also seen (thick arrow in B)

Diagnostic Testing of Lymphomas

- Best initial test for both HL and NHL is excisional lymph node biopsy. Needle biopsy is NOT useful.

Clinical (Ann Arbor staging) of Hodgkin's and Non-Hodgkin's Lymphomas

- Ann Arbor staging includes CXR, CT scan with contrast (chest, abdomen, pelvis and head) and bone marrow biopsy.
- Lymphangiogram and exploratory laparotomy NOT needed.

Stage	Distribution of Disease
I	Single group of LN involved OR Single extralymphatic organ/site (e.g. spleen, thymus, Waldeyer's ring)

Stage	Distribution of Disease
II	2 or more group of LNs on same side of diaphragm OR Localized extralymphatic organ/site
III	Groups of LN on both sides of diaphragm Involved with/without localized involvement of extralymphatic organ/site
IV	Diffuse involvement of one or more organs or sites with/without lymphatic involvement

All stages are further divided on the basis of absence (A) or presence (B) of the following symptoms: unexplained fever; drenching night sweats and/or unexplained weight loss of greater than 10% of normal body weight.

Treatment

- Localized disease (stage I and II) without "B" symptoms are treated with radiation.

- Advanced (stages III and IV) treated with chemotherapy.
- HL: ABVD (Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine)
- NHL: CHOP (Cyclophosphamide, Hydroxyadriamycin, Oncovin (vincristine), Prednisone). Also test for anti-CD20 antigen. If present add rituximab, which adds more efficacy to CHOP.
- Nivolumab (Programmed Death, PD-1 pathway inhibitor) for relapsed refractory lymphomas.

EXTRA EDGE

- For Hodgkin's lymphoma, a weekly chemotherapy regimen administered for 12 weeks called Stanford V is becoming increasingly popular, but it includes radiation therapy, which has been associated with life-threatening late toxicities such as premature coronary artery disease and second solid tumors.

International Prognostic Index (IPI) For NHL

- Five clinical risk factors (these are a/w poor prognosis):
 - Age ≥ 60 years
 - Serum LDH levels elevated
 - Performance status ≥ 2 (ECOG) or ≤ 70 (Karnofsky scale) - i.e., a poor performance
 - Ann Arbor stage III or IV
 - ≥ 1 site of extranodal involvement.

PLASMA CELL DISORDERS

A.k.a monoclonal gammopathies, paraproteinemias, plasma cell dyscrasias, and dysproteinemias. Includes multiple myeloma, MGUS and Waldenstrom's macroglobulinemia as discussed below.

Multiple Myeloma

- Monoclonal plasma cell cancer (fried egg appearance) that arises within the bone marrow and produces large amounts of IgG or IgA.
- Average age = 70 years; MC in blacks, males.
- Clinical features:
 - Back/Bone pain (MC presenting symptom; vertebra is MC site); Unlike the pain of metastatic carcinoma, which often is worse at night, the pain of myeloma is precipitated by movement.
 - Frequent infections (bacterial - pneumonia and pyelonephritis) - due to hypogammaglobulinemia.
 - Hypercalcemic symptoms - renal stones (stones, bones, abdominal moans and psychiatric groans), pathologic fractures, and fatigue.
 - Renal failure (due to hypercalcemia)
 - Anemia. (normocytic, normochromic)

- A/w primary amyloidosis (AL).

Tests in Multiple Myeloma

- Skeletal survey: to detect punched out osteolytic lesions. "MyeLoma = Lytic".
- Serum protein electrophoresis (SPEP) - monoclonal immunoglobulin spike (M spike)
- Serum M protein > 30 g/L
- Plasmacytosis > 10%
- Urine protein electrophoresis - Ig light chains in urine (Bence Jones proteins)
- Peripheral smear - increased rouleaux formation of RBCs; increased ESR
- Serum alkaline phosphatase is normal
- ↑ Serum calcium; ↑ beta-2 microglobulin
- Most specific test is bone marrow biopsy

- Treatment: Lenalidomide or Thalidomide (inhibitor of TNF) with dexamethasone (risk of thromboembolism esp. when used with dexamethasone, doxorubicin or melphalan); Melphalan may be added; Bortezomib (proteasome inhibitor, Sfx = neuropathy) may be used.
- International Staging System: for multiple myeloma relies on two factors, beta-2-microglobulin and albumin; other staging system is Durie Salmon system (no longer used).
- Prognosis:
 - Serum beta-2 microglobulin is the single most powerful predictor of survival in multiple myeloma and can substitute for staging!
 - Poor prognosis is also indicated by chromosome 17p deletion, and translocations t(4;14), (14;16), and t(14;20).

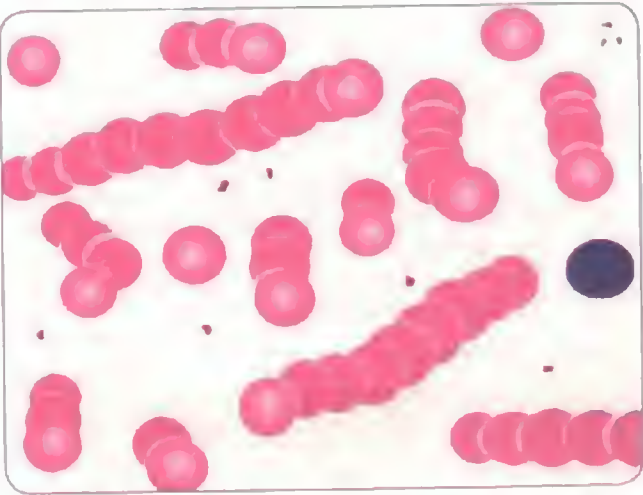


Fig. 11.18: Peripheral blood smear in multiple myeloma showing rouleaux formation

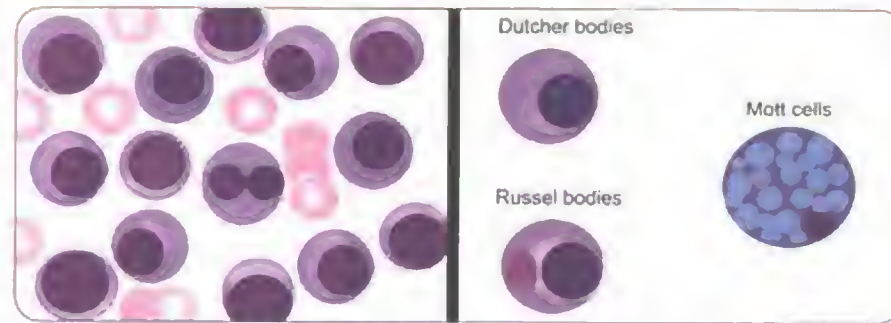


Fig. 11.19: Bone marrow smear showing increased number of plasma cells in multiple myeloma. One binucleate plasma cell and one immature plasma cell with nucleolus are also seen. Panel on right shows some distinctive morphological features of plasma cells

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- **MC plasma cell disorder.**
- M protein in serum **<30 g/L**
- Bone marrow clonal plasma cells **<10%**
- **NO** evidence of other B cell proliferative disorders
- **NO** myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)
- **NO** Bence Jones protein
- Asymptomatic elevation of **IgG** in serum protein electrophoresis;
- **NO** specific intervention is indicated for patients with MGUS. Follow-up once a year or less frequently is adequate except in higher risk MGUS.

Waldenstrom's Macroglobulinemia

- **Elderly male** affected; malignant **B cell** proliferation; Presents with **hyperviscosity** from **IgM overproduction**.
- Serum protein electrophoresis shows **M spike**. **Positive Coomb's test**.
- **In contrast to multiple myeloma** - there are **NO lytic bone lesions**, **NO hypercalcemia** and **NO/rare renal failure**.
- Organomegaly (**hepatosplenomegaly**) is more common; **lymphadenopathy** and **anemia** occurs.
- Increased **rouleaux formation** and **positive Coomb's test**.
- Best initial treatment is **plasmapheresis**; rituximab and bortezomib are effective; **ibrutinib** approved by FDA.
- A distinct **MYD88 L265P** somatic mutation has been reported in over 90% of patients with Waldenstrom's and the majority of IgM MGUS.

Rouleaux Formation

Increased Rouleaux formation	Decreased Rouleaux formation
Caused by increased fibrinogen or globulins in the blood— as in multiple myeloma , hyperfibrinogenemia , Waldenstrom's macroglobulinemia	Due to abnormally shaped RBCs as in hereditary spherocytosis .

- Rouleaux formation of RBC is demonstrated by 'stacking' of RBCs.

Plasmapheresis

- Plasmapheresis may offer benefit and is done in:
 - Waldenstrom's macroglobulinemia.
 - Hemolytic-uremic syndrome
 - Goodpasture's syndrome,
 - Landry Guillain-Barre syndrome
 - ANCA small vessel vasculitis
 - Antiphospholipid syndrome
 - Essential mixed cryoglobulinemia
 - IgA nephropathy
 - Myasthenia gravis
 - Pemphigus vulgaris.

DISORDERS ASSOCIATED WITH THROMBOSIS

Acquired	Inherited
Diseases or syndromes <ul style="list-style-type: none"> • Lupus anticoagulant • Malignancy • Myeloproliferative disorder • Thrombotic thrombocytopenic purpura • Estrogen treatment • Nephritic syndrome • Hyperlipidemia • Hyperviscosity • Diabetes mellitus • Congestive heart failure • Paroxysmal nocturnal hemoglobinuria 	Coagulation factor deficiencies <ul style="list-style-type: none"> • Factor V Leiden • Protein C deficiency • Protein S deficiency • Antithrombin III deficiency Impaired clot lysis <ul style="list-style-type: none"> • Dysfibrinogenemia • Plasminogen deficiency • TPA deficiency • PAI-1 excess Uncertain mechanism <ul style="list-style-type: none"> • Homocystinuria

Physiologic states

- Pregnancy
- Obesity
- Postoperative stage
- Immobilization
- Old age

Bleeding Disorders: Coagulopathy vs Platelet Disorders

	Platelet disorder	Coagulopathy
Bleeding after cuts	Excessive, prolonged	Normal to slightly ↑
Onset of bleeding after injury	Immediate bleeding	Delayed bleeding after surgery or trauma
Clinically	Microhemorrhage; mucus membrane bleeding, epistaxis, Petechiae, Purpura ↑ bleeding time	Macrohemorrhage; deep and excessive bleeding into joints, muscles, GIT and GU tract, easy bruising ↑ PT and/or PTT

DISORDERS OF PLATELETS AND VESSEL WALL

Basics

- **Normal platelet count = 150,000–450,000/μL.**
- The major regulator of platelet production is the hormone **thrombopoietin**, synthesized in the liver.
- **Spontaneous bleeding** occurs when **platelet count falls below 20,000/microl.**
- In a patient with **thrombocytopenia** the target platelet count after platelet transfusion to perform an **invasive procedure is 50,000/microl.**
- Platelet synthesis is increased with **Inflammation** and specifically by **Interleukin 6**.
- Platelets circulate with an average **life span of 7–10 days**.
- **Normal vascular endothelium** contributes to preventing thrombosis by **inhibiting platelet function**.
- When vascular endothelium is injured, these inhibitory effects are overcome, and platelets adhere to the exposed intimal surface primarily through **VWF (Von Willebrand Factor)**. Platelet adhesion results in the generation of intracellular signals that lead to activation of the platelet glycoprotein (Gp) IIb/IIIa (αIIbβ3) receptor and resultant **platelet aggregation**.
- **Endothelial cells** line the surface of the entire circulatory tree, totaling $1-6 \times 10^{11}$ cells, enough to cover a surface area of about six tennis courts!!
- The **endothelium normally presents an antithrombotic surface** but rapidly becomes prothrombotic when stimulated, which promotes coagulation, inhibits hemolysis, and activates platelets.

- **Anticoagulant present in blood collection tubes:**
 - Purple top - EDTA (**ethylenediamine tetraacetic**)
 - Blue top - sodium citrate
 - Green top - heparin

"Pseudothrombocytopenia"

- An **in vitro artifact (in the lab)** resulting from platelet agglutination via antibodies (usually IgG, but also IgM and IgA) when the **calcium content is decreased** by blood collection in **EDTA tubes** used to collect blood for complete blood counts.
- **How to detect if thrombocytopenia is "pseudo"?** - if a low platelet count is obtained in EDTA-anticoagulated blood, a blood smear should be evaluated and a platelet count determined in blood collected into **sodium citrate tube** or **heparin tube**, or a smear of freshly obtained unanticoagulated blood, such as from a finger stick, can be examined.

Drug induced Thrombocytopenia (DIT)

- Etiology: **Quinine, antibiotics, sulfa** drugs etc.
- Mechanism: Due to **antibody-drug-antigen complexes**.
- Presents 3 weeks after starting the drug and usually **resolves within one week** of stopping the drug.

Heparin Induced Thrombocytopenia (HIT)

- Differs from DIT in 2 ways.
- Thrombocytopenia is **NOT usually severe**, with lowest counts rarely **< 20,000/μL**.
- HIT is not a/w bleeding and, in fact, markedly **increases the risk of thrombosis**.
- Mechanism: Immune mediated - due to **anti-heparin/ PF4 antibody**
- HIT occurs **5–14 days** after initiation of heparin
- HIT can occur after exposure to low-molecular-weight heparin (**LMWH**) as well as unfractionated heparin (**UFH**).
- Platelet factor 4 (**PF-4**) **antibodies** are used for diagnosis.
- STOP heparin
- Use **direct thrombin inhibitors—lepirudin, argatroban**.

ITP (Idiopathic Thrombocytopenic Purpura)

- A.k.a **Immune thrombocytopenic purpura**.
- In **children**: it is usually an **acute** disease, **MC** following an **infection**, and with a self-limited course.
- In **adults**: it is a more **chronic** disease.

- Secondary TTP - a/w underlying disorder such as *HIV*, *hepatitis C* or *SLE*.
- Severe thrombocytopenia due to *antiplatelet IgG* antibodies.
- Mucocutaneous bleeding, such as oral mucosa, gastrointestinal, or heavy menstrual bleeding, may be present.
- Thrombosis is very *rare*
- *Normal spleen size*
- Peripheral platelet destruction, ↑ *megakaryocytes*, *megathrombocytes* (abnormally large platelets indicating accelerated thrombopoiesis).
- PT and PTT are *normal*
- Treat with *prednisolone* and if unresponsive *splenectomy*.
- For patients who relapse after splenectomy or in those who have a contraindication to splenectomy, below two drugs may be used
 - Thrombopoietin receptor agonists: *Romiplostim* (SC injection) or *Eltrombopag* (orally), are effective in raising platelet counts in patients with TTP.
 - *Rituximab* (anti CD20).

Thrombotic Thrombocytopenic Purpura (TTP)

- Pentad of findings that include *microangiopathic hemolytic anemia*, *thrombocytopenia*, *renal failure*, *neurologic findings*, and *fever*.
- Pathogenesis: a deficiency of/ or antibodies to, the metalloprotease *ADAMTS13*, which cleaves VWF.
- *Plasma exchange* remains the *mainstay of treatment* of TTP.
- ↑ platelet aggregation → thrombosis → *schistocytes*

DISORDERS OF COAGULATION

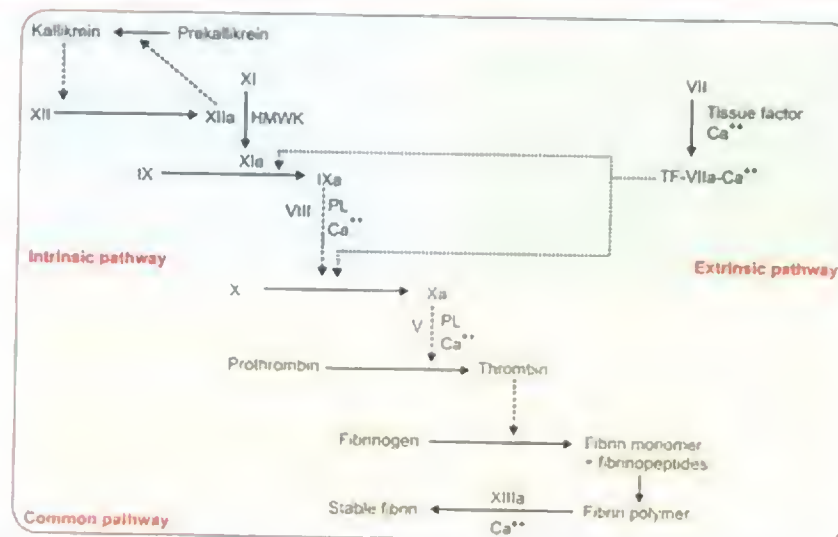


Fig. 11.20: Scheme of blood coagulation. Solid arrows indicate transformation. Broken lines indicate action. Abbreviations: HMWK: High molecular weight kininogen; TF: Tissue factor; PL: Phospholipid; Ca⁺⁺: Calcium

Hemolytic-Uremic Syndrome (HUS)

- HUS is a syndrome characterized by *acute renal failure*, *microangiopathic hemolytic anemia*, and *thrombocytopenia*.
- Seen MC in *children* and after hemorrhagic diarrhea MC due to *E. coli O157:H7*.
- Treatment is mainly *supportive*.

Inherited Platelet Membrane Defects

- *Bernard-Soulier syn.*: Defective platelet *adhesion* absence of *GpIb-IX-V* receptor
- *Glanzmann thrombasthenia*: Defective platelet *aggregation* from an absence of platelet membrane glycoproteins, *GP IIb-IIIa*.
- Both the above are autosomal recessive.

VON Willebrand Disease

- MC hereditary coagulation disorder, AD; Type 1 vWD is MC.
- vWF is a *glycoprotein* that helps in *platelet adherence to vessel wall*.
- A/w Marfan's mitral valve prolapse, angiodysplasia.
- Bruising, *epistaxis*, bleeding symptoms are common *prolonged aPTT*.
- Treat with DDAVP or OCPs (containing estrogen) - this will release *subendothelial stores of vWF and factor VIII* (from *Weibel Palade bodies*).

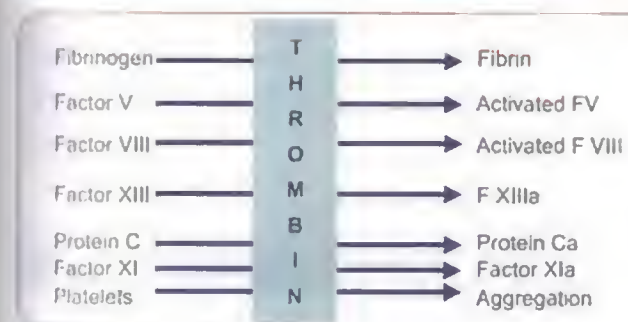


Fig. 11.21: Multiple actions of thrombin in hemostasis

Blood Coagulation Factors

Factor	Synonym
I	Fibrinogen
II	Prothrombin
III	Tissue factor, thromboplastin
IV	Calcium
V	Labile factor, proaccelerin
VI	F VI has been determined to be an activated form of F V and the term factor VI is no longer used
VII	Stable factor
VIII	Antihemophilic factor or globulin
IX	Christmas factor, plasma thromboplastin component
X	Stuart prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor, Laki Lorand factor
Fletcher factor	Prekallikrein
Fitzgerald factor	HMWK (High Molecular weight Kininogen)

Commonly used Tests of Hemostasis

- Isolated *prolonged prothrombin time (PT)* suggests *F VII* deficiency.
- A *prolonged activated partial thromboplastin time (aPTT)* indicates *MC hemophilia or FXI deficiency*.
- *Prolongation of both PT and aPTT* suggests *deficiency of FV, FX, FII, or fibrinogen abnormalities*.

Clotting factor deficiencies and treatment.

Clotting factor deficiency	Treatment
Fibrinogen	Cryoprecipitate
Prothrombin	FFP/PCC
Factor V	FFP

Contd.

Contd.

Clotting factor deficiency	Treatment
Factor VII	FFP/PCC
Factor VIII	Factor VIII concentrates
Factor IX	Factor IX concentrates
Factor X	FFP/PCC
Factor XI	FFP
Factor XII	No Rx (no risk for bleeding)
HMW kininogen	No Rx (no risk for bleeding)
Prekallikrein	No Rx (no risk for bleeding)
Factor XIII	Cryoprecipitate/Factor XIII concentrates

HEMOPHILIA

- *Classic Hemophilia A* (*F8 gene mutation*) and *deficiency of factor VIIIc*.
- *Hemophilia B* (*Christmas disease; F9 gene mutation*); *deficiency of factor IX*.
- Note: *Factor XI deficiency* sometimes called *hemophilia C*!
- Both are *XLR*; Both are clinically indistinguishable.
- Disease more apparent when child begins to crawl/walk - causes *recurrent hemarthroses* and bleeding into *limb muscles*; *hematuria*, *retroperitoneal hemorrhages*, *CNS bleeds*, *gum bleeds* occur
- *Main Treatment: Factor VIII and Factor IX concentrates*; Non transfusion therapy = Intranasal or IV *DDAVP* maybe used for mild bleeds in *Hemophilia A ONLY*; *Antifibrinolytic agents* (*Tranexamic acid*, *E-aminocaproic acid*) in both hemophilia A and B maybe used.

More MCQ points

- *Vitamin K dependant clotting factors*: 2,7,9,10; protein C and S
- Newborns lack bacterial colonisation in bowel; so *NO synthesis of vitamin K*
- *Rat poison* contains *warfarin*.
- Hemorrhagic skin necrosis maybe a/w *warfarin therapy*.
- All clotting factor deficiencies are *autosomal recessive except factor VIII and IX deficiency* (which is *X-linked*).
- The clot formed is not stable unless *extensive cross linking occurs* that is done by *factor XIIIa*.
- The *circulating neutrophils* are usually *mature* and *NOT* clonally derived in *leukemoid reactions*.

Disseminated Intravascular Coagulation (DIC)

Activation of coagulation cascade leading to microthrombi and global consumption of platelets, fibrin, and coagulation factors—leads to hemorrhage which may be difficult to stop.

Causes:

- Snake Venom, Shock, Heat stroke, Aortic aneurysm Nephrotic syndrome.
- Tissue trauma (crush injuries, burns, gunshot wounds, extensive surgery)
- Sepsis-**MC cause** (gram negative, classically meningococemia)
- Liver disease (advanced cirrhosis, fulminant hepatic failure)

- Obstetric complications (preeclampsia, eclampsia, abruptio placentae, septic abortion, retained dead fetus, retained placenta, amniotic fluid embolism)
- Tumors (pancreas, prostate, lung, stomach, AML, breast)
(**"VSHANT play The SLOTS!"**)

Lab findings in DIC

- ↑ PT, ↑ PTT,
- ↑ Fibrin degradation products, FDP (**most sensitive test**)
- D-dimers - most specific for detection of fibrin and NOT fibrinogen,
- ↓ platelet count.
- **Helmet** shaped cells/**schistocytes** on blood smear.

CHAPTER**12****Genetics****CHROMOSOMES****Basics about Chromosomes**

- **ISCN** = International System for human Cytogenetic Nomenclature.
- "**p**" = short arm (*petit*) and "**q**" = long arm; by convention "**p**" arm is always shown on top in the karyotype.
- Nomenclature of chromosome: Example - Xp15.3 means X chromosome; p (short) arm; Region 1; Band 5 and Sub-band 3.
- Human **male** cell = 44 autosomes + 2 sex chromosomes (XY)
- Human **female** cell = 44 autosomes + 2 sex chromosomes (XX)
- The 44 chromosomes are in pairs, the two chromosomes of a pair being exactly alike = **homologous**.
- The **Human Genome Project (HGP)** was completed in **April 2003**. It determined the DNA sequence of the entire human genome.

Term	Description
Haploid	23 chromosomes (e.g. sperm and ovum)
Diploid	46 chromosomes (ex: number of chromosomes in each human cell)
Euploid	When a cell has a multiple of 23 chromosomes
Aneuploidy	Numerical abnormalities of chromosomes (NOT an exact multiple of 23)
Polyploidy	Homologous chromosome numbers in more than two complete sets; ex: 3 sets: triploid (69); 4 sets: tetraploid (92) chromosomes - both lethal conditions

EXTRA EDGE

- Most autosomal **monosomies** are **incompatible** with survival leading to spontaneous abortions
- Autosomal **trisomies** (ex: trisomy 13, 18, 21) are **compatible** with life.
- **Sex chromosomal** monosomies (ex, Turner's 45 XO) and trisomies (Klinefelter's, 47 XXY) are **compatible** with life.
- Correct human chromosome number given by **Tijo and Levan**.

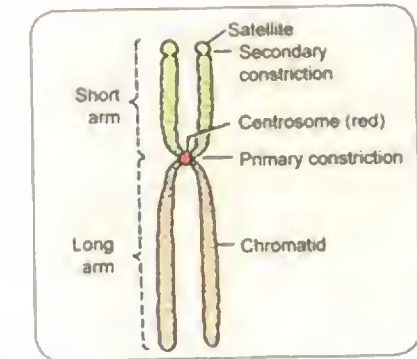


Fig. 12.1: Diagram to show the terms applied to some parts of a typical chromosome. Note that this chromosome is submetacentric.

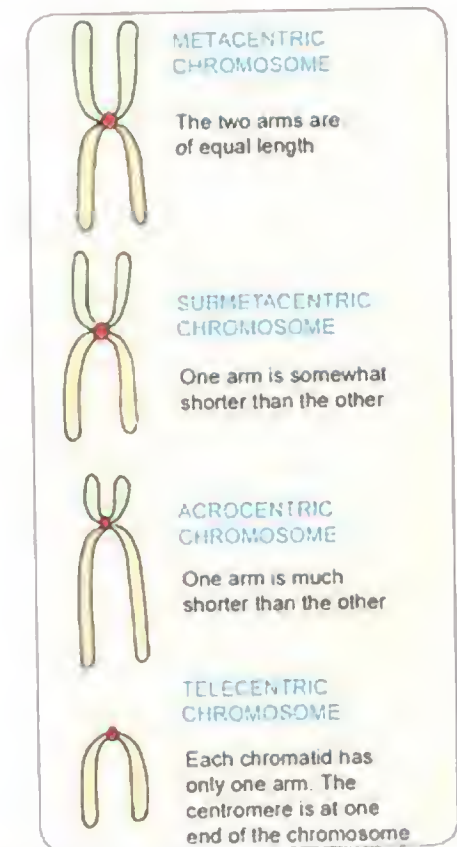


Fig. 12.2: Nomenclature used for different types of chromosomes, based on differences in lengths of the two arms of each chromatid

CYTOGENETIC METHODS

- **Cytogenetics** = Study of human chromosomes.
- **Karyotyping** (chromosomes mapping) = **Photographic** representation of the chromosomal constitution of an individual.
- **Diagrammatic** representation of chromosome morphology indicating **bands and sub-bands** is called an **ideogram**.

How is Karyotyping Done?

- **Human chromosomes** may be visualized in any growing tissue such as *bone marrow, skin fibroblasts, amniotic fluid cells, chorionic villus*, but they are **most conveniently studied in peripheral blood lymphocytes**. (Note: NO karyotyping from monocytes, since they do not divide further and cannot be used for karyotyping)
- A blood sample is drawn and put into a suitable medium in which lymphocytes can multiply.
- After a few hours, a drug which (**colchicin, colcemid**) arrests cell division at a stage when chromosomes are most distinct is added to the medium.
- Remember: Chromosomes are **best seen** during **metaphase** stage of mitosis.
- The dividing cells are then treated with **hypotonic** saline so that they swell up—leading to proper spreading of the chromosomes.
- The suspension containing the dividing cells is spread out on a slide and suitably stained.
- Various stains are used, MC being **Giemsa** (hence called **G-banding**); Euchromatin stains light and heterochromatin stains dark.
- Cells in which the chromosomes are well spread out are **photographed**. These photos are cut out and arranged in proper sequence starting with **largest autosome to the smallest (decreasing order of length)** and finally the sex chromosomes.
- Also Know:
 - **Q banding** uses fluorescent **Quinacrine** stains (used for identifying Y chromosome)
 - **T banding** stains **telomeres**
 - **C banding** stains **centromeres**
 - **R banding** is **Reverse of G banding**.
 - **FuDR banding**—to detect fragile sites in chromosome as in fragile X syndrome.

Other methods of chromosome analysis

- **SKY (Spectral Karyotyping)**: For analysis of **chromosomal rearrangements and translocations**.
- **FISH (Fluorescence in situ Hybridization)**: to detect and **localise specific DNA/gene** sequences and direct visualization of anomalies (e.g. microdeletions—when too small to be detected by karyotyping); **m-FISH = multicolor FISH**.
- **CGH (comparative genomic hybridization)**: To study **unbalanced chromosomal aberrations only**.
- **Feulgen reaction**: It is a staining method for cellular DNA that reacts with Schiff's reagent. It is specific for **2-deoxyribose** sugar.
- **High resolution banding** technique: Similar as karyotyping except treatment with **ethidium bromide or actinomycin D** with short exposure of colchicine.

Denver's Classification of Chromosomes

Group	Type	Chromosome number
A	Metacentric	1–3
B	Submetacentric	4, 5
C	Submetacentric	6–12, X
D	Acrocentric	13–15
E	Submetacentric	16–18
F	Metacentric	19, 20
G	Acrocentric	21, 22, Y

- Denver's classification of human chromosomes arranged the chromosomes into **7 groups (A to G)** on the basis of decreasing length and arm ratio (i.e. based on **size**).
- Chromosomes 1–3 of group **A** and 19, 20 of group **F** are **Metacentric**.
- Chromosomes 13–15 of group **D** and 21, 22 and Y of group **G** are **Acrocentric**.
- **Ridiculous mnemonic** for above - try if it works for you ("**A Forensic Medicine Doctor Gave Anesthesia!!**")
- So, rest of chromosomes (group B, C, E) are **submetacentric**.
- From above you can derive that **X chromosome is submetacentric** and **Y is acrocentric**.

EXTRA EDGE

- Five chromosome pairs viz, 13, 14, 15, 21, 22 and Y possess satellite bodies - hence also called **sat-chromosomes**. These are concerned with organization of nucleoli.
- Also know that, chromosome **X** belongs to group **C** and **Y** belongs to group **G** ("**seXC GuY!!**").

STRUCTURAL CHROMOSOME ABNORMALITIES

1. Inversions

- Here a segment of a chromosome has broken away and the rejoined in the same position but rotated through **180 degrees**.
- This usually has **NO phenotypic effect** (i.e. no clinical manifestation).
- Maybe **pericentric** or **paracentric**

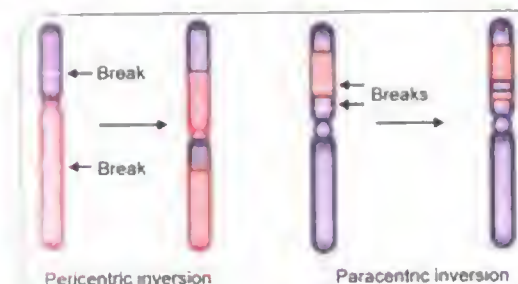


Fig. 12.3: Inversion

2. Deletion

- A segment of chromosome may break off and be lost.
- Deletions large enough to be seen with light microscope are usually lethal.
- Submicroscopic deletions are **detected by FISH**.
- Chromosomal deletion syndromes are mentioned below:

Chromosomal segment deleted	Syndrome
4p	Wolf-Hirschhorn syndrome
5p	Cri-du-chat syndrome
5q	Soto syndrome
7q	Williams syndrome
11p	Beckwith-Wideman syndrome
13q	Retinoblastoma syndrome (with mental retardation and dysmorphic facies)
15q	Angelman and Prader Willi syndrome
16p	Rubinstein Taybi syn. (microcephaly, broad thumbs, big toes, mental retardation)
17p	Smith Magenis syndrome
22q	Di George syndrome, Velocardiofacial syndrome

3. Isochromosomes

- During mitotic cell division, the chromosome divides longitudinally; rarely it may divide transversely across the centromere—half of the chromosome replicates to form its complement.

- Thus two new types of chromosomes are formed, **one having both long arms** and the other with **both short arms** - these are **isochromosomes**, i.e. a chromosome in which one arm is lost and the other remaining arm is reduplicated.

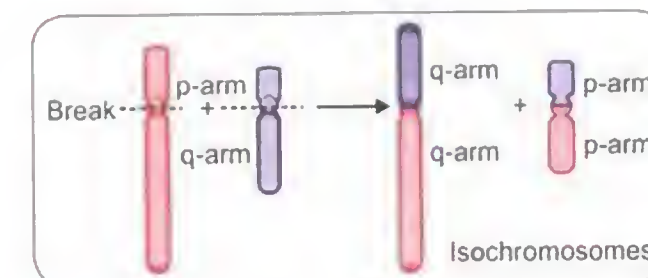


Fig. 12.4: Isochromosomes

4. Translocation

- Translocations occur when chromosomes are broken and the broken elements reattach to other chromosomes.
- **Reciprocal translocation** occurs when genetic material is exchanged between two non-homologous chromosomes (ex chromosome 3 and 8); maybe of two types—balanced and non-balanced.
 - **Philadelphia chromosome** t (9; 22) in CML is an example of reciprocal translocation.
- **Robertsonian translocations** are much **more common**. They occur **only in acrocentric** chromosomes (13, 14, 15, 21, 22) and involve the loss of short arms of two chromosomes and subsequent fusion of the long arms.
 - Approximately **5% of Down's syndrome** are result of Robertsonian translocation affecting **chromosome 14 and 21**.

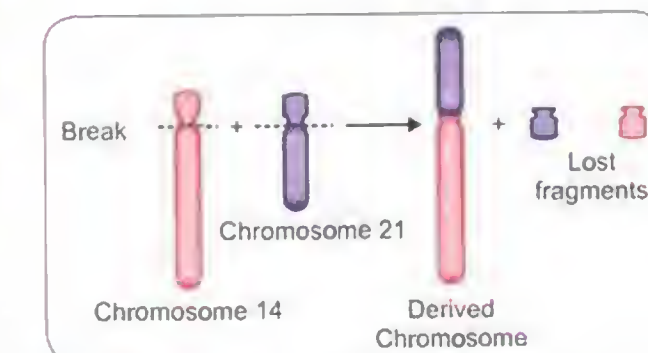


Fig. 12.5: Robertsonian translocation

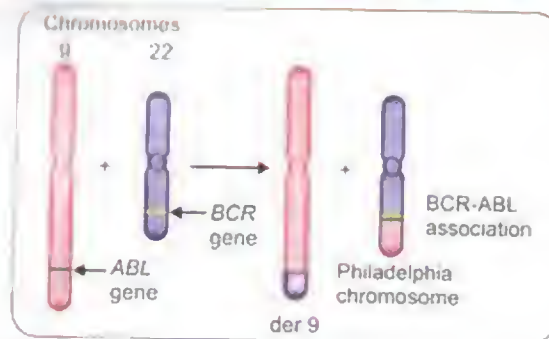


Fig. 12.6: Reciprocal translocation

5. Ring Chromosome

- This can form when a deletion occurs on both tips of the chromosome and the remaining sticky chromosome ends fuse together.
- Ring chromosomes are often lost resulting in a *monosomy*.

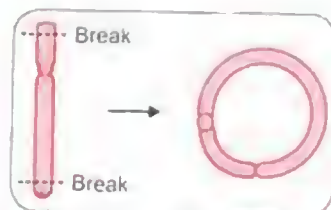


Fig. 12.7: Ring chromosome

NUMERICAL CHROMOSOME ABNORMALITIES

1. Non-disjunction

- The *failure* of two members of chromosome to separate during cell division, so that both pass to the same

daughter cell; this is the **MC cause of aneuploidies** including Down, Edward, Patau, Turner and Klinefelter syndromes.

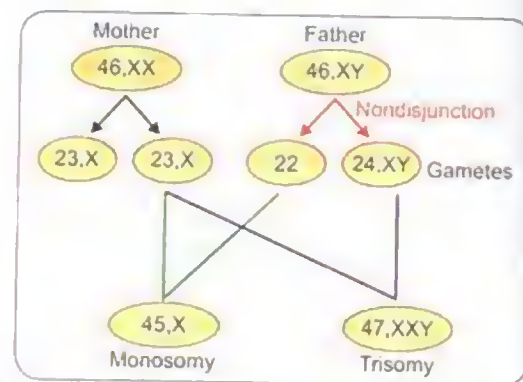


Fig. 12.8: Mechanism of nondisjunction

2. Anaphase Lag

- In the first meiotic division, the chromosomes are arranged in pairs in the equatorial plane during the metaphase. During anaphase if one of the chromosomes is slow in its migration, it might be excluded and thus lost.

Chromosomal breakage syndromes

- **Blaauw's syndrome** (congenital telangiectatic erythema with dwarfism)
- **Xeroderma pigmentosum**
- **Fanconi's anemia** (constitutional aplastic pancytopenia)
- **Ataxia telangiectasia**

GENE LOCATION OF CERTAIN DISEASES ON CHROMOSOMES

Chromosomes	Diseases
Chromosome 1	Contains the most known genetic diseases (890 total) of any human chromosome. Alzheimer disease, Charcot Marie-Tooth disease, Galactosemia, Gaucher disease, Homocystinuria, Prostate cancer.
Chromosome 2	Genes on chromosome 2 may play an important role in human intelligence . Alport syn., Amyotrophic lateral sclerosis, Ehlers-Danlos syn., HNPCC
Chromosome 3	Alkaptonuria, Von Hippel-Lindau syn., susceptibility/resistance to HIV infection.
Chromosome 4	Achondroplasia, Huntington's disease . (Hunt 4 CAGe! —same mnemonic later in this chapter)
Chromosome 5	Familial Adenomatous Polyposis is caused by a deletion of the APC tumor suppressor gene on 5q. (FAP = Five) Cri-du-chat syn. is caused by partial deletion of 5p (5p-). " 5 pussy c(h)ats ".
Chromosome 6	Major Histocompatibility Complex (MHC) ("MHC = MH6! C resembles 6") AR polycystic kidney disease, porphyria cutanea tarda

Contd.

Chromosomes	Diseases
Chromosome 7	Contains the Homeobox A gene cluster. Cystic fibrosis (7q) ; " 7 quite cysters ", Williams syn. (7q)
Chromosome 8	Burkitt's lymphoma ; " (B looks like 8) ", Schizophrenia
Chromosome 9	Friedreich ataxia, tuberous sclerosis, inheritance of blood groups , HOCM
Chromosome 10	Hirschsprung disease
Chromosome 11	More than 40% of olfactory receptor genes are located here. Ataxia-telangiectasia, Beckwith-Wiedemann syn., multiple endocrine neoplasia type 1, WT1 gene
Chromosome 12	Contains the Homeobox C gene cluster. Tyrosinemia, Noonan syndrome
Chromosome 13	Retinoblastoma (13q14) , Wilson disease, Trisomy 13 (Patau's syn.)
Chromosome 14	α -1 antitrypsin deficiency, Familial HOCM, Meniere's disease
Chromosome 15	Angelman syndrome and Prader-Willi syn - 15q
Chromosome 16	AD polycystic kidney - (has " 16 letters "), pseudoxanthoma elasticum, Autism.
Chromosome 17	Contains the Homeobox B gene cluster. Li-Fraumeni syn. (p53 on 17p) (" LI inverted = 17 "), Neurofibromatosis type 1; BRCA-1 (17q)
Chromosome 18	Trisomy 18 (" Edward's syn = Eighteen ")
Chromosome 19	Peutz-Jeghers syndrome (AD); Insulin Receptor, Myotonic dystrophy
Chromosome 20	Adenosine deaminase deficiency (SCID), Alagille syndrome DM Type 1
Chromosome 21	Smallest human chromosome. Acute myeloid leukemia (AML)—t (8; 21) Trisomy 21 - Down's syn. —extra chromosome 21 due to non-disjunction .
Chromosome 22	First human chromosome to be fully sequenced. Philadelphia chromosome is a/w CML—t(9; 22)(q34; q11). CATCH 22 syn. (microdeletions of 22) Neurofibromatosis type 2 (= chr 22)

EXTRA EDGE

- Initially chromosome 22 was thought to be the smallest - remember in a karyography, chromosomes are arranged from largest to smallest and hence theoretically, 22 should be smallest; however, with improved karyotyping techniques **chromosome 21 was found to be the smallest!**—but no effort was made to change the numbering since by then chromosome 21 was already strongly a/w Down's syndrome!

PRENATAL DIAGNOSIS

Chorionic Villus Sampling (CVS)

- Transabdominal or transcervical aspiration of **chorionic villus tissue** at under ultrasound guidance.
- Done between **10-13 weeks (12 weeks)**.
- Uses
 - To detect fetal chromosomal, biochemical and cytogenetic disorders.
 - CVS does **NOT** detect neural tube defects.
- Complications

- NOT done < 9 weeks due to higher **limb amputation** rates and **cleft palate**.
- Abortion rates = 1-2% (**more than for amniocentesis**)
- Amniotic fluid leak (**oligohydramnios**) may occur.

Amniocentesis

- Transabdominal or transcervical aspiration of needle aspiration of amniotic sac under ultrasound guidance.
- Done > **16 weeks**. About **30 ml** fluid is collected.
- Uses
 - To determine the fetal karyotype (preferred for chromosomal studies);
 - **ALSO detects neural tube defects and chromosome disorders with greater sensitivity** than triple screen alone.
 - Therapeutic uses: Induction of abortion (by instilling chemicals); rapid decompression of polyhydramnios; amniocentesis in oligohydramnios;
- Complications
 - **NOT performed before 15 weeks** due to risk of **abortion (0.5%)** and higher **talipes** rates

Triple and Quadruple Test (Quad Test)

Triple test	Quadruple test
Maternal serum α-fetoprotein (MSAFP)	Triple test
+	+
unconjugated estradiol (UE3)	maternal serum dimeric inhibin A (DIA)
+	
human chorionic gonadotropin (hCG)	

	MSAFP	UE3	hCG	DIA
Down's syndrome	↓	↓	↑	↑
Edward's syndrome	↓	↓	↓	N

- These are screening tests for *Down's syndrome*.
- Performed in ALL pregnant women **between 16–18 weeks** of gestation.
- **Serial Integrated test** = Quad test + PAPP-A.

Classification of Genetic disorders

1. Mutations
2. Mendelian disorders
3. Chromosomal disorders
4. Other patterns of inheritance
5. Disorders of sex differentiation

Disease	Gene	Locus	Protein	Repeat
Expansions affecting non-coding regions				
Fragile X syndrome	FMRI (FRAXA)	Xq27.3	FMR-1 Protein (FMRP)	CGG
Friedrich ataxia	FXN	9q21.1	Frataxin	GAA
Myotonic dystrophy	DMPK	19q13.3	Myotonic dystrophy protein kinase (DMPK)	CTG
Expansions affecting coding regions (CAG)				
Huntington's Disease	HTT	4q16.3	Huntingtin	CAG
Spinobulbar muscular atrophy (Kennedy disease)	AR	Xq12	Androgen receptor	CAG
Dentatorubral Pallidoluysian atrophy (Haw River syndrome)	ATNL	12p13.31	Atrophin-1	CAG
Spinocerebellar ataxia (Types 1,2,3,6,7)			Ataxin	CAG

EXTRA EDGE

- Spinocerebellar ataxia (SCA) **type 3** is **Machado-Joseph** disease.
- Mnemonic: ("**Hunt 4 CAGe**") - **Huntington's** disease (**CAG** repeats on chromosome **4**)

MUTATIONS

- Mutations are **permanent changes in DNA**. The types and examples are given in below table.

Point mutations	
Silent mutation	Here, the codon changes BUT forms the same amino acid (e.g. CUA is mutated to CUC, both code for leucine and so the mutation has No effect on the phenotype).
Missense mutation	(Sickle cell trait/disease): A change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene
Nonsense mutation with stop codon	(Beta thalas- semia major): Here the altered DNA sequence prematurely signals the cell to stop building a protein (replacement of amino acid by a stop codon)

Frameshift mutations

- (**Tay-Sachs disease**): This mutation occurs when the addition or loss of DNA bases changes a gene's reading frame

TRINUCLEOTIDE REPEAT DISEASES

- These are mainly **neuro-degenerative diseases** caused by a **dynamic mutation** that is an expansion of a repetitive sequence of three nucleotides.
- The length of the expansion continues to increase as cells divide throughout life (**somatic instability**).
- May show **genetic anticipation** (disease severity and age of onset-in successive generations).

Fragile-X Syndrome

- **MC** inherited cause of mental retardation
- Non-staining gap on the **long arm of X chromosome** designated **Xq 27.3**; **CGG triplet repeat**;
- **Large testes (macroorchidism)**,

- **Long thin face with large everted ears, large jaw and Autism.**
- ("Tingile X = eXtra large - testes, jaw, ears")

EXTRA EDGE

- **Penetrance:** The percentage of individuals with a given genotype (disease-causing mutation) who manifest the phenotype (i.e. actually develop the disease).
- **Incomplete penetrance:** Not all individuals with a mutant genotype shows the mutant phenotype. *Example:* BRCA-1 gene mutations do NOT always result in breast and ovarian cancer
- **Variable expressivity:** The trait is seen in individuals carrying the mutant gene BUT is expressed differently among individuals, e.g. [patients of **NF-1** have varying severity from just brown skin spots to multiple skin tumors in different patients]; also seen in **MEN-1**; **cystic fibrosis** and **Alzheimer's disease**.

MENDELIAN DISORDERS

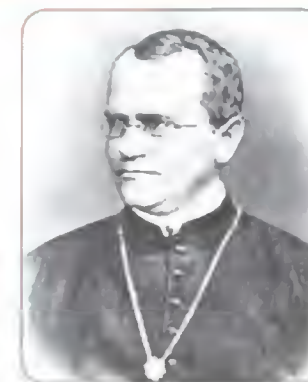


Fig. 12.9: Mendel

Basics

- **Proband (or propositus):** The **family member who first presents** with a given trait.
- **Punnett square:** The **Punnett square** is a **diagram** that is used to predict an outcome of a particular cross

or breeding experiment (Aa and aa as shown in the below table). It is used by biologists to determine the probability of an offspring having a particular genotype (to determine the **recurrence risk** of a genetic disease appearing in the offspring).

	A	a
a	Aa	aa
a	Aa	aa

- **Genotype:** The genetic constitution of an individual, usually at a particular locus.
- **Phenotype:** The characteristics of an organism which result from an interaction between gene (the genotype) and environment.
- **MC type of Mendelian disorder is Autosomal Dominant.**

Symbols used in Pedigree Charting



Fig. 12.10: Pedigree symbols

Autosomal dominant (AD)	Autosomal recessive (AR)
Due to defects in structural genes	Due to enzyme deficiencies
One dominant mutant gene (A) is required to express the disorder	Individuals must be homozygous for the mutant recessive gene (aa) to express the disorder
Homozygotes are spontaneously aborted	Homozygotes are symptomatic early in life
Heterozygotes (Aa) express the disorder	Heterozygotes (Aa) are asymptomatic carriers
Offspring of an affected parent have a 50 per cent chance of being affected (Disease cannot be transmitted through unaffected parents)	Both parents must be heterozygous to transmit the disorder
Example: Aa X aa = Aa, Aa, aa, aa (50% with disorder; 50% normal)	Example: Aa X Aa = AA, Aa, Aa, aa (25% without disorder; 50% asymptomatic carriers; 25% with disorder)

Contd.

Autosomal dominant (AD)	Autosomal recessive (AR)
NO carrier state	Carrier state exists
"Vertical" inheritance	"Horizontal" inheritance (since many siblings affected).
X-linked recessive	X-linked dominant
A family history of the condition may exist—the gene responsible is transmitted by affected man to all his daughters and 50 per cent of the daughter's sons , sometimes called " knight's move " transmission.	
Incidence and severity in males is much higher	Affects both sexes, but females more than males
No male-to-male transmission	
X-linked recessive	X-linked dominant
Condition is transmitted by carrier women	
Affected males have only normal sons and carrier daughters	All children of affected homozygous females are affected
Females with only one X-chromosome, e.g., (Turner's syn.) can manifest X-linked recessive disorders in the same way as males do.	Females pass the trait to half their sons and half their daughters
For example, Hemophilia (types A and B), color blindness, Becker's muscular dystrophy, G-6-PD deficiency, Menkes kinky hair syn., Wiskott-Aldrich syn., Fabry's disease	All daughters of affected males are affected, but none of their sons
	Examples of X-linked dominant diseases are incontinentia pigmenti, vitamin D resistant (hypophosphatemic rickets), blood group Xg, Alport's syndrome , etc.

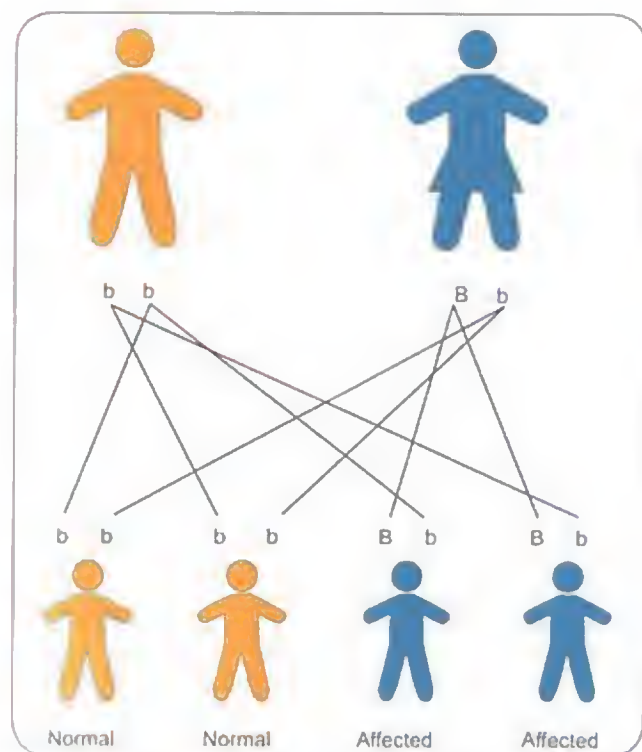


Fig. 12.11: Autosomal dominant condition: One parent is affected, 'B' is the gene with the dominant mutation. Example: Huntington's disease.

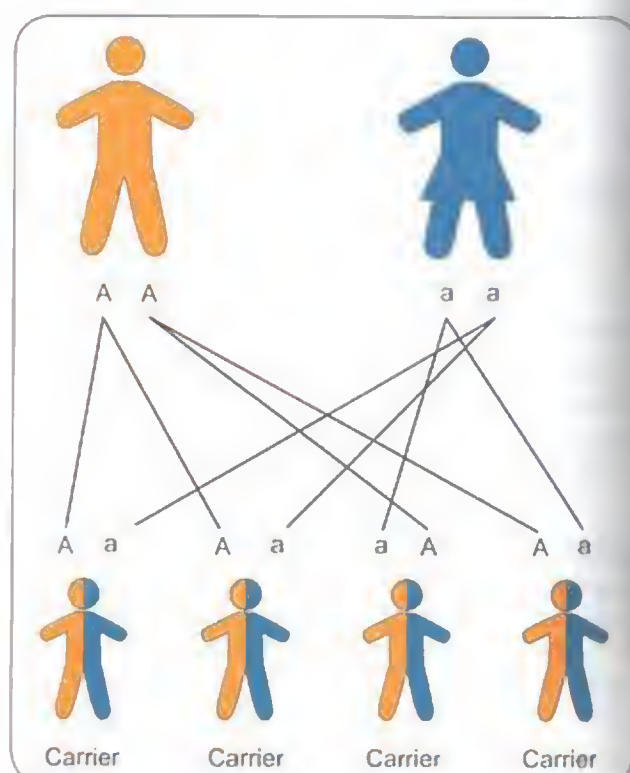


Fig. 12.12: Autosomal recessive conditions: One parent is affected, 'a' is the gene with the recessive mutation.

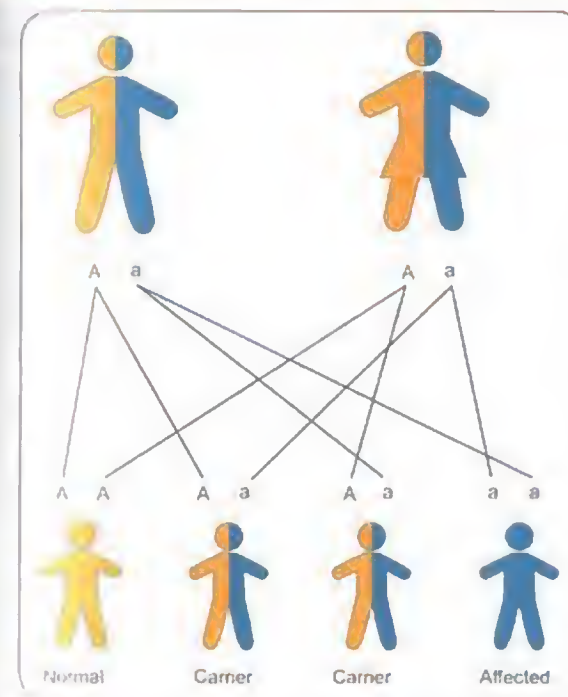


Fig. 12.13: Autosomal recessive conditions: Both parents are carriers, 'a' is the gene with the recessive mutation. Example: Cystic fibrosis.

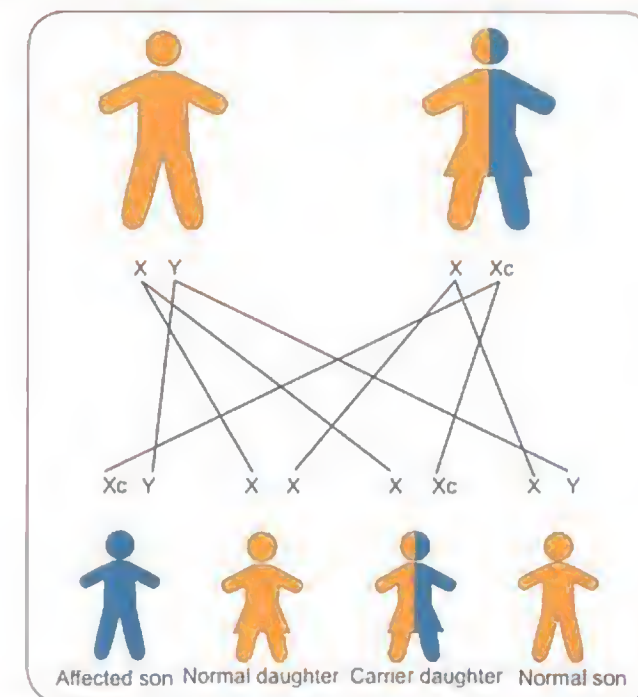


Fig. 12.15: X-linked recessive conditions: Mother is a carrier, 'Xc' represents the gene mutation on the X chromosome. Example: Hemophilia.

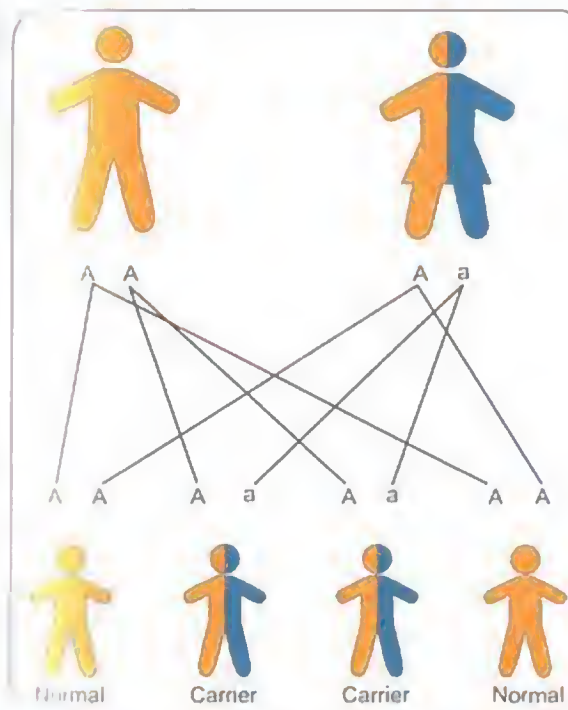


Fig. 12.14: Autosomal recessive conditions: One parent is a carrier, 'a' is the gene with the recessive mutation.

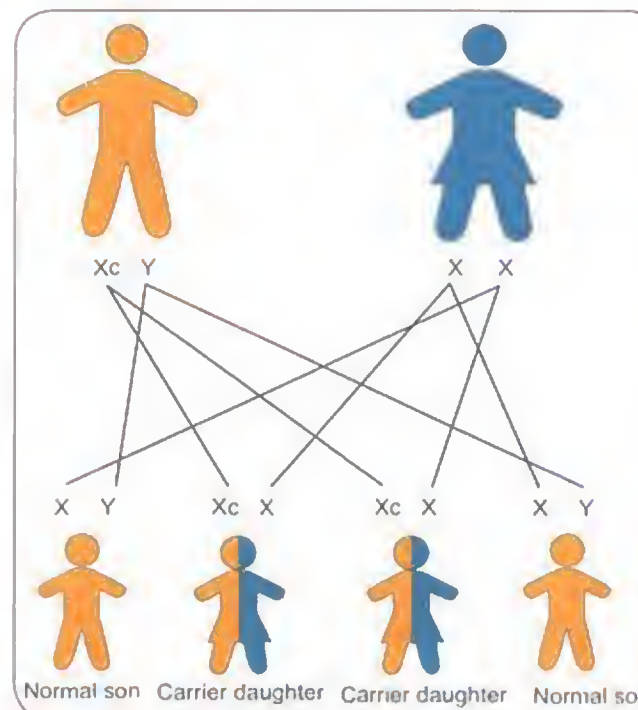


Fig. 12.16: X-linked recessive conditions: Father is affected, 'Xc' represents the gene mutation on the X chromosome.

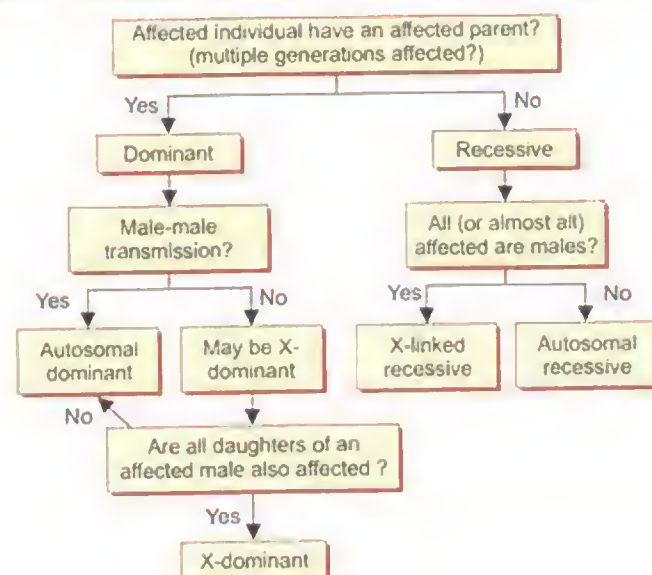


Fig. 12.17: Decision tree

EXTRA EDGE

- If transmission occurs **ONLY** through affected mothers and **NEVER** through affected sons, the pedigree is likely to reflect **mitochondrial** inheritance.
- In AD disorders, there may be **reduced penetrance** and **variable expressivity**.

Inherited Monogenic/Single Gene/Mendelian Disorders

System	Autosomal dominant	Autosomal Recessive	X-linked recessive
Skeletal	Marfan's syndrome Ehler-Danlos syndrome (some variants) Osteogenesis imperfecta Achondroplasia	Ehler's-Danlos syndrome (some variants) Alkaptonuria	Duchenne muscular dystrophy
Nervous	Huntington's disease Neurofibromatosis Myotonic dystrophy Tuberous sclerosis	Friedrich ataxia Neurogenic muscular atrophies Spinal muscular atrophy	Fragile-X syndrome
Metabolic	Familial hypercholesterolemia Acute intermittent porphyria	Cystic fibrosis Phenylketonuria Galactosemia Homocystinuria Lysosomal storage diseases o-1 antitrypsin deficiency Wilson disease Hemochromatosis Glycogen storage disease	Hunter's syndrome Diabetes insipidus Lesch-Nyhan syndrome
Hematopoietic	Hereditary spherocytosis Von Willebrand disease	Sickle cell anemia Thalassemias	Hemophilia A and B Chronic granulomatous disease G-6- PD deficiency
Others	Familial polyposis coli Polycystic kidney disease Romano Ward syndrome	Congenital adrenal hyperplasia	Agammaglobulinemia Wiskott-Aldrich syndrome

EXTRA EDGE

- Most **structural abnormalities** are **AD**. Also diseases with prefix "hereditary/familial" are usually AD.
- Most **enzymatic/biochemical** abnormalities (inborn errors of metabolism) are **AR**. (Exceptions are G6PD deficiency, Hunter's disease and Fabry's disease - **XLR**)

CHROMOSOMAL DISORDERS**Down's Syndrome**

- A.k.a **Trisomy 21, mongolism**
- It is **MC aneuploidy** and **MC trisomy**
- Incidence more with ↑ **maternal age** (commonly above 35 years); Incidence at 30 yrs = 1:800 live births; at 35 yrs = 1:270; at 40 yrs is 1:100 and at 45 yrs is 1:50.
- Extra chromosome 21** due to **non-disjunction**
- Mental retardation** (MC genetic cause of MR), **short stature**, **hypotonia (floppiness)**, **upward-slanting eyes**, **epicanthic folds**, **low-set ears**, **flat occiput**, **Brushfield spots on iris**, **macroglossia**, **single palmar (simian) crease**.
- Associated anomalies: **congenital heart disease** (MC is **ostium primum ASD**, a.k.a AV septal defect or endocardial cushion defect); **obstructive sleep apnea**, **tracheoesophageal fistula**; **gastrointestinal (duodenal atresia, Hirschsprung's)**; **leukemia**, **hypothyroidism**; more tendency for early **Alzheimer's disease**; **reduced life expectancy**

- HbF level increased.**
- Life expectancy < 1 year.**

Edward's Syndrome (Trisomy 18)

- ("Edwards = Eighteen")
- Prominent occiput**, **low-set ears**, **micrognathia**.
- 'Rocker-bottom' feet**.
- Mental retardation**.
- Ocular signs are rare.**
- Cardiac, renal malformations.**
- Clenched hand with overlapping index and fifth fingers.**
- Quadruple test:** As in table above.
- Life expectancy < 1 year**



Fig. 12.18: Down's syndrome

Prenatal diagnosis of Down's syndrome

- Triple test** (at 14 weeks) and **Quadruple test**: as in table under prenatal diagnosis topic later in this chapter
- PAPP-A** (Pregnancy-associated placental protein-A) (in 1st trimester)
- Neutrophil alkaline phosphatase
- To diagnose Down's syndrome in 1 trimester, a combination of beta hCG, PAPP-A and nuchal translucency is used.

Ultrasound Markers (11–20 weeks):

- Nuchal translucency** (thick nuchal fold > 3 mm thick).
- Hyperechogenic fetal bowel**
- Choroid plexus cysts**
- Hyperechogenic foci** ('goof balls') in the fetal heart.
- Double bubble** in abdomen.
- Short femur or humerus**.
- Clinodactyly**.
- Renal pyelectasis** (bilateral renal pelvic dilation).
- Fetal ECHO: A-V conal defects**

EXTRA EDGE

- Achondroplasia** is o/w increased **Paternal age** ("A: chondroPlasia - Aged Pappa").

Patau's Syndrome (Trisomy 13)

- Cleft lip and Palate**,
- Holoprosencephaly**,
- Polydactyly**,
- Microphthalmia**,
- congenital heart disease**,
- high frequency of aberrant projections on neutrophil lymphocytes.**



Fig. 12.19: Patau's syndrome



Fig. 12.20: Edward syndrome

'Cri Du Chat' Syndrome

- 46 XY or 46 XX; chromosome 5p-.
- Mental retardation, spasticity, **high pitched cat-like cry**, micrognathia, low-set ears, and epicanthic folds

'Catch 22' Syndrome

- Variable presentation as **DiGeorge syn.** (thymic, parathyroid and cardiac defects) or **velocardiofacial syn.** (palate, facial and cardiac defects)
- "CATCH" = Cleft palate, Abnormal facies, Thymic hypoplasia (T cell deficiency), Cardiac defects, Hypocalcemia (secondary to parathyroid aplasia).
- "22" = microdeletions at chromosome 22q11.

William's Syndrome

- Chromosome 7q; **Elfin facies**;
- **Over friendliness with strangers also !**;
- Mental and growth retardation; (BUT verbally well developed)
- **Idiopathic hypercalcemia**, renal stones,
- Squints,
- CVS (supravalvular **aortic stenosis**).

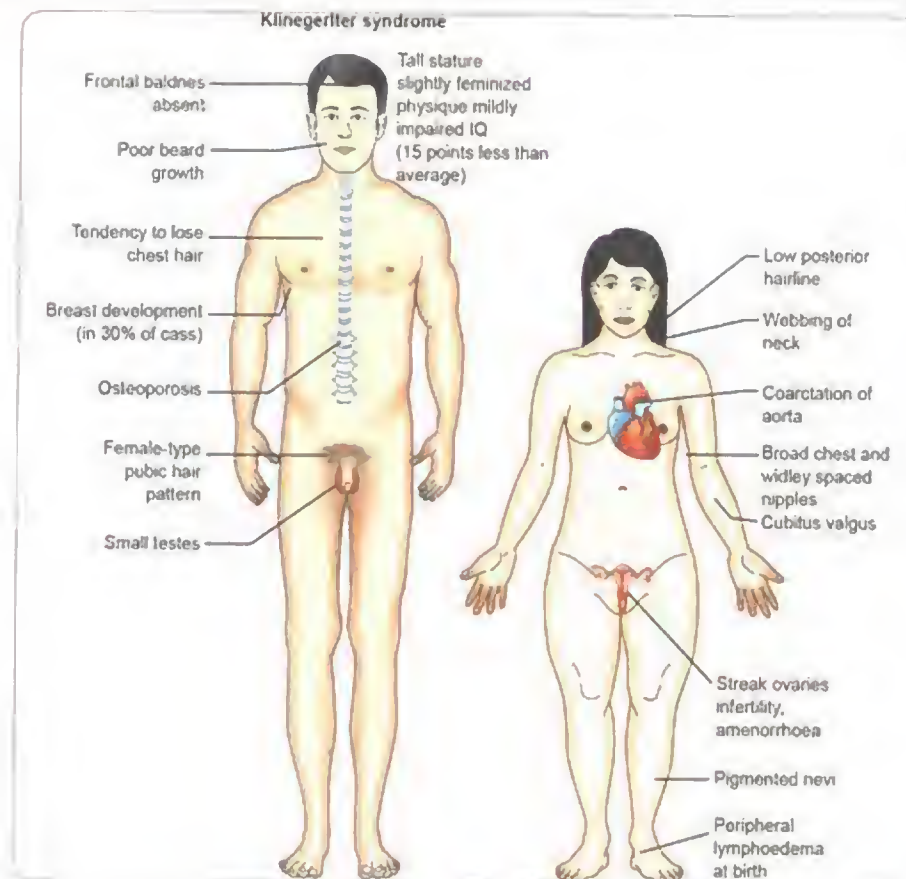


Fig. 12.21: Klinefelter's and Turner's syndromes

Turner's syndrome	Klinefelter's syndrome	Noonan's syndrome
45 XO	47 XXY	45 XY
Phenotypically Female	Male	Male
No sex chromatin (Barr body)	One or two sex chromatin (Barr bodies).	One sex chromatin (Barr body)
<ul style="list-style-type: none"> • Short stature, • Wide carrying angle, • Webbing of neck, • Lymphedema of dorsum of hands and feet, cystic hygroma, • Short metacarpals (retarded bone age), • Shield like chest with widely spaced nipples. • Scanty pubic and axillary hair • Streak ovaries • Primary amenorrhea; • Renal anomalies (horseshoe kidney, double or cleft renal pelvis) • Sensori- neural deafness. • CVS - MC is bicuspid aortic valve > Coarctation of aorta (Nelson textbook of pediatrics, 20th edn/Pg 2744) 	<ul style="list-style-type: none"> • Tall thin Men, • Gynecomostia • Infertility due to hypogonadism— (small testes), • Eunuchism • Testicular tumors • Mentally subnormal • Criminal behavior • Decreased testosterone and inhibin and • Increased LH and FSH 	<ul style="list-style-type: none"> • Similar features to Turner's—a.k.a., Male Turner's! • Absent testis • CVS - MC is pulmonic stenosis

MITOCHONDRIAL INHERITANCE

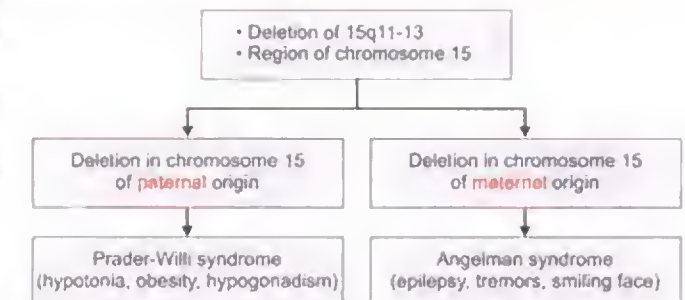
- Mitochondrial DNA (**mt DNA**) mutates **10 times more frequently** than nuclear DNA; as there are **no introns**, a mutation will invariably strike a coding sequence.
- **Maternal inheritance:** Transmitted **ONLY through mother** (no mtDNA transmitted through sperms).
- Normal and mutant mt DNA may coexist within one cell (**heteroplasmy**)
- Often due to failure in **oxidative phosphorylation**.
- **Poor genotype-phenotype correlation.**

Diseases a/w mitochondrial inheritance

- Mitochondrial Encephalopathy Lactic Acidosis and Stroke- like episodes (**MELAS**)
- **Lebers hereditary optic neuropathy**
- **NARP** (Neuropathy, ataxia, retinitis pigmentosa), Myoclonic Epilepsy with Ragged Red Fibres (**MERRF**)
- **Sensorineural** deafness
- Mitochondrial **myopathy**
- **Keorns Soyre** syndrome
- **Pearson** syndrome.

MORE GENETICS TOPICS**Uniparental Disomy**

- A condition where both chromosomes of a pair have been inherited from **only one parent** (maternal or paternal). See Prader Willi and Angelman's syndromes below.

Flowchart 12.1: Genomic imprinting

Mnemonic: P for paternal and Prader-Willi; Angelman and mother—she is our angel

Imprinting

- At single locus, only 1 allele is active; the other is inactive (imprinted/inactivated by **methylation**). Deletion of the active allele → disease.
- Prader Willi and Angleman syndromes are due to mutation or deletion of genes on chromosome 15.
- These diseases can also occur as a result of **uniparental disomy (UPD)**-25% of **Prader Willi** and 5% of **Angelman** syndromes are due to **UPD**.

Prader-Willi syndrome	Angelman's syndrome
Paternal allele NOT expressed on chromosome 15q (SNRPN gene and NECDIN gene) - hence called paternal UPD .	Maternal allele not expressed on chromosome 15q (UBE3A gene) - hence called maternal UPD .

Contd..

Contd...

Prader-Willi syndrome	AngelMan's syndrome
<ul style="list-style-type: none"> Mental retardation Extreme obesity (hyperphagia, high ghrelin) Hypogonadotropic hypogonadism Muscle hypotonia Short stature; small hands and feet Hyperflexibility Autonomic dysregulation Adult onset diabetes mellitus Almond shaped eyes 	<ul style="list-style-type: none"> Seizures Ataxia (wide based gait - resembles marionette - a puppet) mental Retardation Inappropriate laughter (happy puppet) "SARI"
<ul style="list-style-type: none"> Mnemonic: Prader Willi - no Paternal allele; AngelMan- No Maternal allele. Other examples of imprinting: <ul style="list-style-type: none"> ➤ Beckwith-Wiedemann syndrome (11p15). ➤ Russell Silver syndrome. ➤ Transient neonatal diabetes. 	

EXTRA EDGE

- Beckwith-Wiedemann syndrome:** Affects *children*; chromosome **11p15** affected; macrosomia (**gigantism**); **macroglossia** (large tongue); **omphalocele** (umbilical hernia); **organomegaly**; **neonatal hypoglycemia**; increased risk of Wilm's tumor (**nephroblastoma**) and **hepatoblastoma**.
- Russell Silver syndrome:** Chromosome 7 affected; short stature; low birth weight; body asymmetry; triangular small face; clinodactyly of the fifth digit.

GLOSSARY

Alleles	Alternative forms of a gene found at the same locus on a particular chromosome.
Barr body	All X chromosomes in excess of one per cell are inactivated so that only one is active (Lyon hypothesis) , which is visible in interphase as a dark-staining Barr body, i.e. no Barr body in male or XO female.
cDNA	A single-stranded DNA that is complementary to an mRNA and is synthesized from it by the enzyme reverse transcriptase <i>in vitro</i> ; often used as a probe in chromosome mapping.
Chimera	An individual composed of two populations of cells from different genotypes , e.g. blood group chimerism.
Chromatids	Equal halves of a chromosome following replication.
Cloning	The isolation of a particular gene or DNA sequence. In recombinant technology, genes or DNA sequences are cloned by inserting them into a bacterium or other microorganism, which is then selected and propagated.
Concordant twins	Members of a pair of twins exhibiting the same trait.
Conserved sequence	A DNA sequence that has remained virtually unchanged throughout evolution . This is usually taken to imply that the sequence has an important function.
Codominance	Both alleles contribute to the phenotype of the heterozygote; Ex: Blood groups A, B, AB; alpha-1 antitrypsin deficiency

Contd

Contd

Cosmid	A plasmid into which the DNA sequences from bacteriophage lambda that are necessary for the packaging of DNA have been inserted; this permits the plasmid DNA to be packaged <i>in vitro</i> .
Degeneracy	A genetic code in which some amino acids may each be encoded by more than one codon .
Deletion	A chromosomal aberration in which part of the chromosome is lost.
Discordant twins	Only one twin has the trait.
Dizygotic twins	Twins produced by two separately fertilized ova.
Endonuclease	An enzyme that cleaves internal bonds in DNA or RNA.
Exonuclease	An enzyme that cleaves nucleotides from either the 3' or 5' ends of DNA or RNA.
Exon	Portion of the DNA that codes for the final mRNA and is then translated into protein.
Gene	A region of DNA that encodes a protein
Genome	The complete set of genes of an organism and the intervening DNA sequences. The Human Genome Project is an international research programme aimed at mapping all the genes in the human genome.
Heteroploidy	Abnormal appearance of the karyotype due to alteration in the (i) number of chromosomes or (ii) their shape and form.
Heteroplasmy	Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.
Hybridization	The joining of the complementary sequences of DNA (or DNA and RNA) by base pairing.
Index case	Same as proband
In situ hybridization	Use of a labelled probe to detect any complementary DNA or RNA sequence in a tissue section, cultured cell or cloned bacterial cell.
Insert	An additional length of base pairs in DNA, generally introduced by techniques of recombinant DNA technology.
Intron	Intervening sequence on DNA that is excised before translation.
Locus	Site of a gene on a chromosome
Lyonization	Inactivation of one X chromosome occurs on the 16th day of life.
Meiosis	Sex cell division or reduction division. Formation of gametes with half the number of chromosomes (haploid) as the parent cell (diploid): i.e. 23.
Mitosis	Somatic cell division: Each daughter cell has the same complement of chromosomes as the parent: i.e. 46.
Monozygotic twins	Twins produced from a single fertilized ovum .
Phage	Virus that multiplies in bacteria
Plasmid	An autonomously replicating DNA element, separate from the chromosome . These units, which only occur in bacteria, can be used as vectors of small fragments of foreign DNA.
Pleiotropy	The production of multiple effects by a single gene.
Reverse transcription	DNA synthesis from RNA templates, catalysed by the enzyme reverse transcriptase. It is used to synthesize DNA for probes and occurs naturally in retroviruses.
Splicing	The removal of introns from messenger RNA and the joining together of adjacent exons.
Tandem repeat sequences	Multiple copies of a short DNA sequence lying in a series along a chromosome; used in physical mapping, linkage mapping and also in DNA fingerprinting because each person's pattern of tandem repeats is likely to be unique.
Transfection	The transfer of new genetic material into cells.
Transduction	Bacteriophage mediated gene transfer
Translocation	The transfer of genetic material from one chromosome to another non-homologous chromosome.
Transposition	Movement from one site in the genome to another.
Transposon	A segment of DNA that can move from one position in the genome to another
Vector	A DNA molecule, usually derived from a virus or bacterial plasmid, which acts as a vehicle to introduce foreign DNA into host cells for cloning, and then to recover it.

CHAPTER

13

Biostatistics

MEASUREMENT

Measures of Central Tendency

Measures	Description
Arithmetic mean	Sum of observations divided by number of observations; Mean = $\Sigma x/n$
Geometric mean	Calculated using first the logarithm of the values, then the arithmetic mean of the logarithm and finally the antilog of the calculated arithmetic mean.
Median	The central value of a series of observations arranged in order of magnitude. Unlike the mean, it is NOT sensitive to extreme values in a series.
Mode	The most frequently observed value in a series.

Measures of Dispersion

Range	<ul style="list-style-type: none"> The difference between the highest and lowest values
Quantiles	<ul style="list-style-type: none"> The level of measurement below which a specified proportion of the distribution falls, e.g. the 5th and 95th percentile are the values of a particular measurement below which 5% and 95% of people fall. Percentile divides a distribution into 100 equal parts; quartile into 4 equal parts; tertile into 3 equal parts; ...similarly, hexile, heptile, octile, decile.
Standard deviation (SD)	<ul style="list-style-type: none"> Measure of spread of observations about the mean $S.D = \sqrt{\text{Sum of (Individual observations - mean)}^2 / \text{Number of observations}}$
Coefficient of variation	<ul style="list-style-type: none"> Ratio of the standard deviation of a series of observations to the mean of the observations. It is without units and is expressed as a percentage. Coefficient of variation (%) = $SD/\text{Mean} \times 100$

Mean deviation

- Average of absolute differences (differences expressed without plus or minus sign) between each value in a set of values, and the average of all values of the set. For example, the average (arithmetic mean or mean) of the set of values 1, 2, 3, 4, and 5 is $(15 \div 5)$ or 3. The difference between this average (3) and the values in the set is 2, 1, 0, -1, and -2; the absolute difference being 2, 1, 0, 1, and 2. The average of these numbers $(6 \div 5)$ is 1.2 which is the mean deviation. Also called **mean absolute deviation**, it is used as a measure of dispersion where the number of values or quantities is small, otherwise standard deviation is used.

Variance

- Variance measures how far a set of numbers is spread out. A variance of zero indicates that all the values are identical. An equivalent measure is the square root of the variance, called the standard deviation.

EXTRA EDGE

In a distribution with extreme values (outliers):

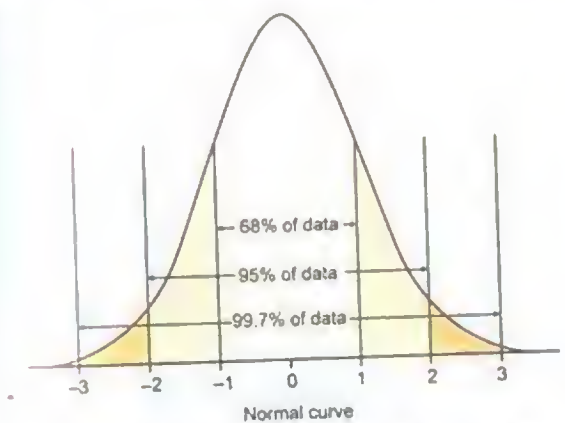
- Most affected measure of central tendency = Mean
- Least affected measure of central tendency = Mode
- Most preferred measure of central tendency = Median

Measures of Skewness

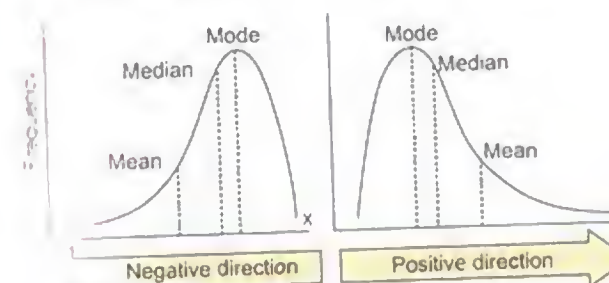
- These help us to find out the direction and extent of asymmetry in a series. They may either be absolute or relative.
- 3 important measures of measuring skewness:
 - Karl Pearson's method
 Pearson's mode or first skewness coefficient = $\text{Mean} - \text{Mode} / \text{SD}$
 Pearson's median or second skewness coefficient = $3(\text{Mean} - \text{Median}) / S$
 - Bowler's method
 - Kelly's method

Statistical Distribution

Measure	Description
Normal curve	Gaussian = Bell-shaped curve (mean = median = mode). Total area of the curve = 1, Mean = zero; SD = 1. Approximately 68% of the observations fall within one SD of the mean; 95% of observations fall within two SD from the mean and 99% fall within three SD from the mean.
Bimodal	2 humps; Mode = 3 Median - 2 mean
Positive (right) skew	Mean > median > mode. Asymmetry with right tail longer
Negative (left) skew	Mean < median < mode. Asymmetry with left tail longer
Binomial Distribution	This describes the probability distribution of possible outcomes from a series of data when there are: Only two mutually exclusive outcomes, e.g. success or failure, boy or girl.
Poisson Distribution	This describes the probability of occurrence of rare events in a large population. It represents a limiting case of the binomial distribution, e.g. the probability of occurrence of a specific congenital birth defect in a large number of births.



(a) Negatively skewed (c) Positively skewed



Confidence Interval

- Confidence Interval (CI) is the interval within which a parameter value is expected to lie with certain expected confidence levels, as could be revealed by repeated samples.
- Larger the sample size, narrower is the CI.
- Smaller the SD, narrower is the CI.

Hypothesis

- Null hypothesis (H_0): Hypothesis of no association (e.g., there is no association between the disease and the risk factor in the population)
- Alternative hypothesis (H_1): Hypothesis of some association (e.g., there is some association between the disease and the risk factor in the population)

Errors in Studies

Type I error

- The null hypothesis is true but is rejected (i.e., false positive)
- Probability of type 1 error is given by "P" value
- Significance (alpha, α) level: is the maximum tolerable probability of type 1 error.
- Keep type 1 error to be minimum; then results are declared to be statistically significant.
- Type 1 error is more serious than type 2 error.
- The null hypothesis is false but is not rejected / accepted (i.e., false negative)
- Probability of type 2 error is given by (beta, β).

Power of a Test

- Power of a statistical test = $1 - \beta$ (1 - probability of type 2 error)
- Power is a numerical representation of sensitivity
- Power can be increased by
 - Increasing sample size
 - Increasing sensitivity
 - Reducing β (probability of type 2 error)

Accuracy and Precision

- Accuracy refers to the closeness of a measured value to a known or standard value.
- Precision refers to the closeness of two or more measurements to each other.
- Example: Imagine a basketball player shooting baskets. If the player shoots with accuracy, his aim will always take the ball close to or into the basket. If the player shoots with precision, his aim will always take the ball to the same location (which may or may not be close to the basket). A good player will be both accurate and precise by shooting the ball the same way each time and into the basket!

Scales of Measurement

Categorical scales (qualitative)

Nominal scale

Based on NOM (names); no specific order

Examples:

- Race
- Religion
- Country of birth
- Clinical features
- Hair color
- Sites of lymphadenopathy
- Sex of child
- Type of anemia
- Site of malignancy
- ABO blood group

Ordinal scale

Based on ORD (order); grading into categories

Examples:

- TNM staging
- Severity of a disease
- Social classes
- Hamilton depression scale; mini mental scale
- Likert scale (1 = strongly disagree; 2 = disagree; 3 = neutral; 4 = agree; 5 = strongly agree)

Dimensional scales (quantitative)

Metric scale

Examples: Blood glucose; hemoglobin level; serum cholesterol; weight; height; mid-arm circumference; BP; pulse rate; temperature.

Kaplan-Meier Survival Curve

- The **Kaplan-Meier survival curve** is an estimator for estimating the survival function from life-time data.
- In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment.
- An important advantage of the Kaplan-Meier curve is that the method can take into account some types of censored data, particularly **right-censoring**, which occurs if a patient withdraws from a study, i.e. is lost from the sample before the final outcome is observed.

Bland Altman Plot

- The **Bland-Altman plot**, or difference plot, is a graphical method to **compare two measurements techniques**. In this graphical method the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques.

Delphi Method

- It is a 'systematic interactive forecasting method' for obtaining consensus forecasts from a panel of independent experts.

Tests of Significance

Parametric tests Student's t-test, Analysis of variance (ANOVA), Pearson correlation

Nonparametric tests χ^2 (Chi-square) test, Fischer's exact probability test, Wilcoxon rank sum test, Wilcoxon signed rank test, McNemar's, Friedman, Cochran's test, Mann Whitney U-test; Spearman correlation

t-test (Student's t-test)

Checks **difference between the means** of 2 groups

ANOVA

Checks the difference **between the means of 3 or more** groups

χ^2 test

Check difference **between 2 or more percentages or proportions** of categorical outcomes (not mean values). r is always between -1 and $+1$. The **closer the absolute value of r is to 1, the stronger is the correlation** between the 2 variables.

Coefficient of correlation (r)

Probability value (p value)

If $p < 0.05$ the null hypothesis can be rejected (i.e., there is a significant relationship between the 2 groups)

Data Representation

Quantitative Data

Histogram
Frequency polygon
Frequency curve
Line chart/graph
Cumulative frequency diagram
Scatter/Dot diagram

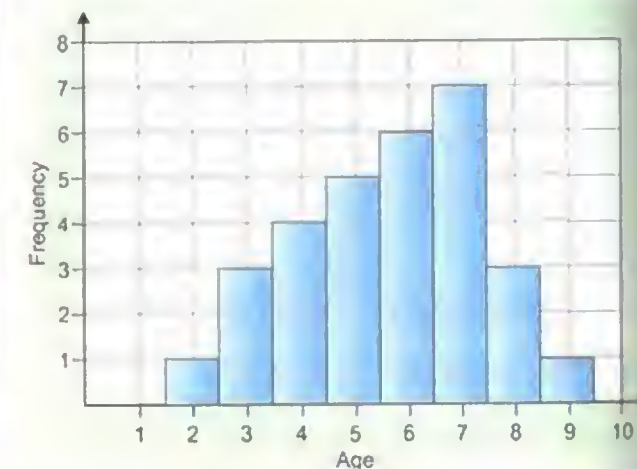
Qualitative Data

Bar diagram
Pie/Sector diagram
Pictogram
Map diagram

GRAPHIC REPRESENTATION

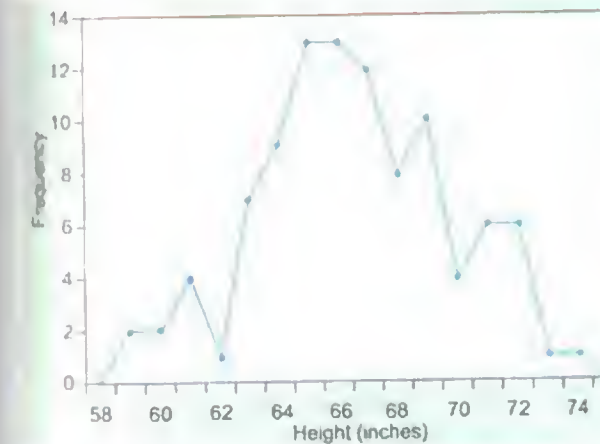
Histogram

Is graphical representation of continuous quantitative data. Continuous groups are marked on X axis (abscissa) and frequencies are marked on Y axis (ordinate).



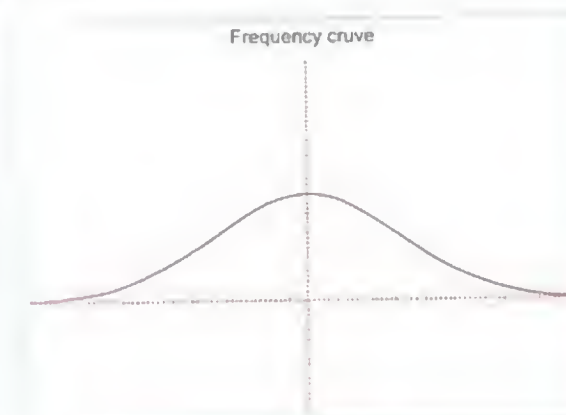
Frequency Polygon

Is an area diagram of frequency distribution over a histogram; made by joining the mid points of class intervals at the heights of frequencies.



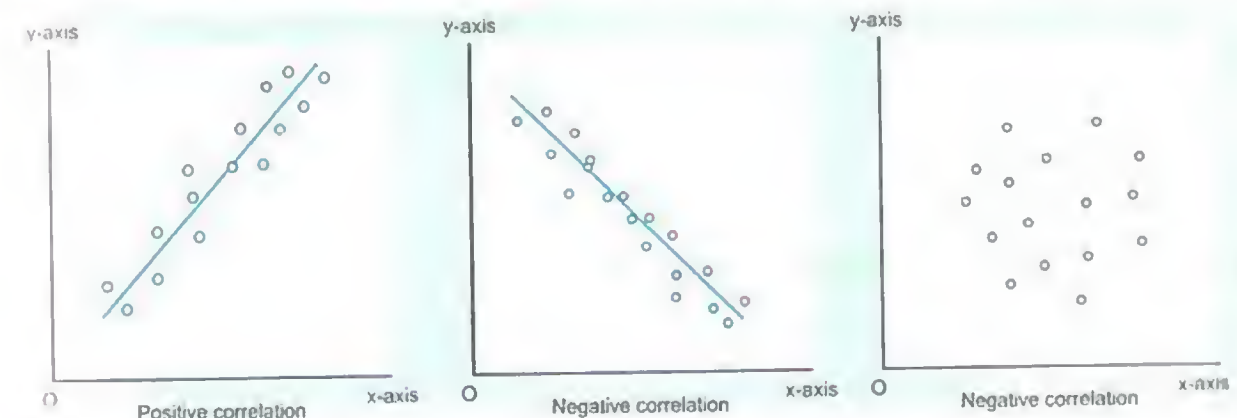
Frequency Curve

When the number of observations is large and group-interval is reduced, frequency polygon loses its angulations and becomes a curve.



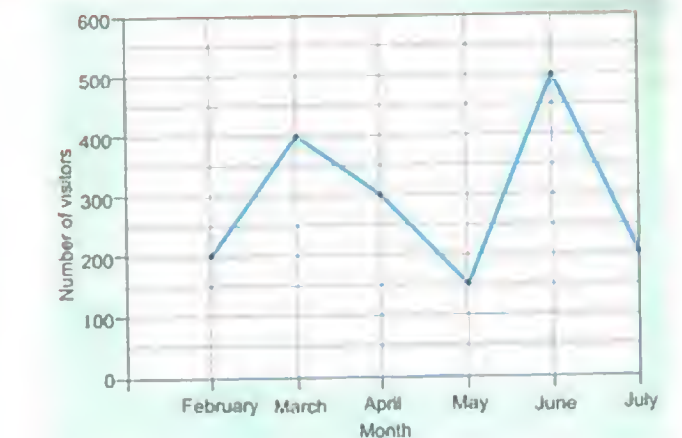
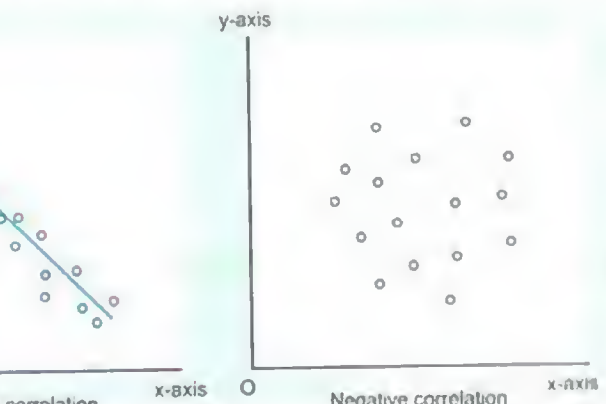
Line Chart/Graph

It is a frequency polygon representing variations by lines; it shows the trend of an event over a period of time.



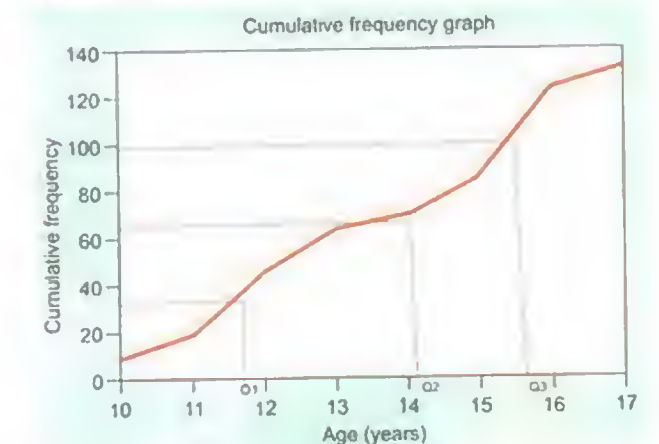
Scatter/Dot Diagram

A.k.a correlation diagram; it is used to depict correlation between two quantitative variables; vertical axis should be dependent on the outcome variable.



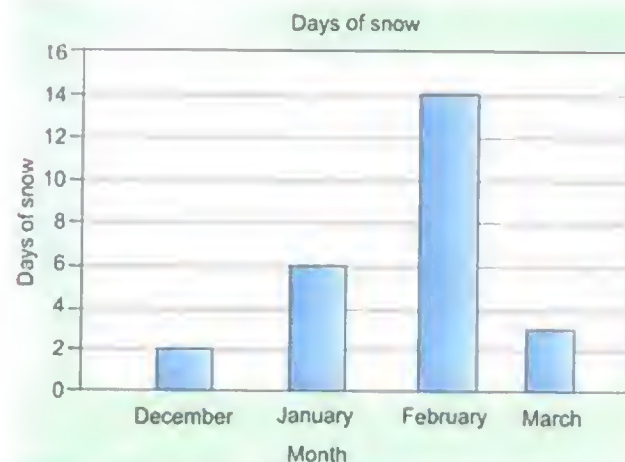
Cumulative Frequency Diagram (Ogive)

Is a graph of cumulative frequency distributions.

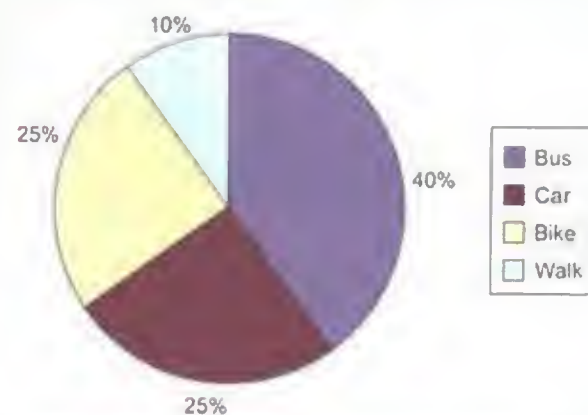


Bar Diagram

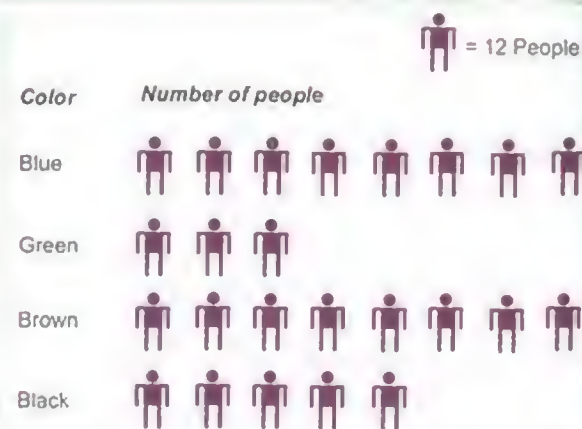
Is for comparison of different frequencies in a data visually; It is the most versatile of all statistical diagrams.

**Pie/Sector Diagram**

Is for presentation of discrete data of qualitative characteristics; all pie categories are mutually exclusive with a total of 100% (360 degrees).

**Pictogram**

It is a method to impress the frequency of occurrence of events to common man.

**Map Diagram/Spot Map**

Is prepared to show geographical distribution of frequencies of characteristics; each spot (dot) marks one frequency; superimposed on map of state/district/country etc.

**CHAPTER****14****Preventive and Social Medicine****PRIMITIVE MEDICINE****Ayurveda System of Medicine**

- Ayurveda means '*Science of Life*'
- '*Tridosha*' theory of disease: Disease occurs when there is disequilibrium in three *doshas* (*humors*), namely, *Vata* (wind), *Pitta* (gall) and *Kapha* (mucus).

Unani System of Medicine

- Originated from *Greece*
- Based on the '*humoral theory*': *Blood*, *phlegm*, *yellow bile* and *black bile*
- Patient's character: *Sanguine*, *phlegmatic*, *choleric* and *melancholic*.

Siddha System of Medicine

- Siddha means '*achievement*'
- Is practiced in *Tamil* speaking parts in India and abroad
- Based on notion that medical treatment has to take into account the patient's *environment*, *age*, *sex*, *race*, *physiological constitution* etc.

Homeopathy System of Medicine

- Founding Father of Homeopathy: *Samuel Hahnemann* (*Germany*)
- Principles of Homeopathy:
- 1st principle - '*similia similibus curentur*': Homeopathy is system of pharmacodynamics based on treatment of disease by use of small amounts of a drug that, in healthy persons, produces symptoms similar to those of the disease being treated (known as: Human drug pathogenicity study')
- 2nd principle: *Single medicine* at the time of treatment
- 3rd principle: *Minimum dose* to be used.

EXTRA EDGE

- The above ISM&H (Indigenous System of Medicine and Homeopathy) have been now re-designated as '*AYUSH* system' of medicine: *Ayurveda*; *Yoga* and *Naturopathy*; *Unani*; *Siddha*; *Homeopathy*.

Theories in Public Health

- *Germ theory* of disease: Louis Pasteur
- *Multi-factorial* causation of disease: Pattenkoffer
- *Spontaneous generation* theory: Aristotle
- Theory of *web of causation*: McMahon and Pugh
- Theory of *Contagion*: Hieronymus Fracastorius.

IMPORTANT PEOPLE IN PUBLIC HEALTH

- **Edward Jenner**: Developed first vaccine (for Small pox); coined the term 'Vaccination'
- **John Salk**: First Polio Vaccine
- **Alexander Fleming**: Penicillin (First antibiotic)
- **David Morley**: Growth Chart
- **Samuel Hahnemann**: Invented homeopathy;
- **Karl Landsteiner**: Blood group types
- **James Lind**: Citrus fruits in prevention of Scurvy
- **Walter Reed**: Transmission of Yellow fever;
- **Ronald Ross**: Life cycle of Plasmodium
- **Dhanvantari**: Hindu God of Medicine;
- **Sushruta**: Father of Indian Surgery; wrote *Sushruta samhita*
- **Charaka**: Father of Indian Medicine
- **Hippocrates**: Father of (Modern) Medicine; rejected superstitions about supernatural forces causing illness; First true epidemiologist; first to describe clubbing
- **Ambroise Paré**: Father of (Modern) Surgery
- **John Snow**: Father of Modern Epidemiology; from England; studied Cholera and established the role of drinking water in its spread.
- **Aristotle**: Father of Biology
- **Gregor Mendel**: Father of Genetics
- **Vesalius**: Father of (Modern) Anatomy
- Cholera: Father of public health (is a disease, not a person!)

IMPORTANT BOOKS IN PUBLIC HEALTH

- *Air, Water and Places*: Hippocrates
- *Ayurvedic Text Nidana*: Madhav
- *Charaka Samhita*: Charaka
- *Susruta Samhita*: Susruta (it was translated by Hessler)

- The Canon of Medicine: Avicenna
- The Book on Healing: Avicenna
- Antiseptic Principle of the Practice of Surgery: Joseph Lister.

First "Country" Achievements

- First country to start **family planning** programme: India
- First country to start **blindness control** programme: India
- First country to establish **finger printing bureau**: India (Calcutta, 1897)
- First country to **socialize medicine** completely: Russia
- First country to introduce **compulsary sickness insurance**: Germany

FEW IMPORTANT DISEASES IN PUBLIC HEALTH

- 5-day fever: Trench fever
- 8th day disease: Tetanus neonatorum
- 100-day cough: Pertussis (Whooping cough)
- Father of Public Health: Cholera
- Barometer of Social Welfare: Tuberculosis
- Slim Disease: HIV/ AIDS
- Black Sickness: Kala Azar (Leishmaniasis)
- Black Death: Plague
- Cerebrospinal fever: Meningococcal meningitis
- Brain Fever: Japanese Encephalitis
- Break-bone fever: Dengue
- Monkey fever/disease: KFD (Kyasanur Forest Disease)
- Koch's disease: Tuberculosis
- Hansen's disease: Leprosy
- Rubella: Measles
- Rubula: Mumps.

TYPES OF MEDICINE

- **State Medicine:** Provision of free medical services to the people at government expense
- **Socialized Medicine:** Provision of medical and professional education by the state (as in state medicine), but the programme is operated and regulated by professional groups rather than by government:
 - Prevents competition between practitioners and clients
 - Provisions of medical services supported by state government
 - Ensures social equity that is universally operated by professional health services.
- **Social medicine:** Study of the social, economical, environmental, cultural, psychological and genetic factors, which have a bearing on health.

International Classification of Diseases, 10th revision/edition [ICD-10]

- *ICD-10 is an abbreviation for the International Statistical Classification of Disease and Related Health Problems (10th revision)*
 - Uniform classification for morbidity and mortality data in world
 - ICD is revised every 10 years
- *ICD-10 came in 1993: It covers disease, illness and injuries*
- *ICD-10 is arranged in 22 chapters (ICD-10-CM has 21 chapters)*
- *ICD-10 is arranged in 3 volumes*
 - Volume 1: Classifications, lists, nomenclature and definitions
 - Volume 2: Instruction manual
 - Volume 3: Alphabetical index
- *Codes U 00–U 49: New diseases of uncertain etiology*
- *Codes U 50–U 99: Used in research.*

HEALTH AND WELL-BEING

WHO Definition of Health

- **WHO [1948] definition of health:** *Health is a state of complete physical, mental and social well being, and not merely an absence of disease or infirmity; (recently amplified to include- and an ability to lead a socially and economically productive life)*
 - Is an 'idealistic goal rather than a realistic proposition'
 - It does not regard health as a dynamic concept (human as a state).

Standard of Living

- **Standard of Living:** *Refers to the usual scale of our expenditure, goods we consume and services we enjoy.*
- **Standard of living [WHO] includes:**
 - Income and occupation
 - Standards of housing, sanitation and nutrition
 - Level of provision of health, educational, recreational and other services
- *Standard of living depends on 'Per capita GNP'*

"LIFE" INDICATORS

Physical quality of life index (PQLI)

- Infant mortality rate
- Life expectancy at age 1
- Literacy ("ILL")
- PQLI in India is 65 (2014);
- **Kerala has high PQLI**

Human Development Index (HDI)

- **Longevity** (life expectancy at birth)
- **Income** (real GDP per capita or purchasing power)
- **Knowledge/Education** (adult literacy rate & mean years of schooling); "**LIKE**".
- HDI ranges from **0 to 1**; HDI of **0.8 and over** (very high development); **0.7-0.79** (high development); **0.5-0.69** (medium development); **< 0.5** (low development)
- HDI for **India is 0.624** - **medium HDI** category - **ranking is 131** in the world (for 2016)
- **Rank 1** belongs to **Norway** > **Rank 2, Switzerland and Australia**. (As per the latest 2016 UN Human development report").

Global Hunger Index (GHI)

- The four components are:
 - the % of the population that is **undernourished**,
 - the % of children under five years old who suffer from **wasting** (low weight for height),
 - the % of children under five years old who suffer from **stunting** (low height for age), and
 - the % of children who die before the age of five (**child mortality**).
- In 2016 - India **ranked 97** in the Global Hunger Index

Sullivan's Index

- Expectation of life **free of disability**.
- Computed by subtracting from the life expectancy the probable duration of bed disability and inability to perform major activities.
- One of the most advanced indicators currently available

Disability Adjusted Life Year (DALY)

- It expresses **years of life lost to premature death and years lived with disability** adjusted for the severity of the disability. One DALY is one lost year of healthy life.
- Measure used to express **global (overall) burden of disease**

Health Adjusted Life Expectancy (HALE)

- It is based on life expectancy at birth but **includes an adjustment for time spent in poor health**. It means equivalent number of years in full health that a newborn can expect to live based on current rates of ill health and mortality.

Life Expectancy at Birth

- **Life expectancy** at birth: Average is **68.3 years** (69.9 years for women and 66.9 years for men; i.e. F>M).

Socio-economic Indicators

- Housing
 - Family size
 - Literacy rate
 - Availability per capita calorie
 - GNP per capita
 - Growth rate
 - unemployment level
 - Dependency ratio
- [Mnemonic: "**He FLAGGED**"]

NATURAL HISTORY OF DISEASE

Iceberg Phenomenon of Disease

- Disease in a community may be compared to an iceberg
- **Floating tip:** What physician sees in community (**Clinical cases**)
- **Vast submerged portion:** *Hidden mass of disease* (Latent, inapparent, pre-symptomatic and undiagnosed cases and carriers)
- **Line of demarcation (water surface):** Is between apparent and inapparent infections.
- '**Epidemiologist**' is concerned with '**Hidden portion of iceberg**' whereas **clinician** is concerned with '**Tip of iceberg**'.
- '**Screening**' is done for '**Hidden portion of iceberg**' whereas '**diagnosis**' is done for '**tip of iceberg**'.
- Iceberg phenomenon of disease is NOT shown by: **Measles, Tetanus, Rubella, Rabies (MTR)**.

Prepathogenesis Phase of Disease

- Is period before onset of disease in man (man at risk)
- **Epidemiological triad:** Interaction between **agent, host and environment**
- Primary level of prevention is possible.

Pathogenesis Phase of Disease

- Begins with '**Entry of organism**' in susceptible host
- **Multiplication** of organism, disease initiation and progression
- Final outcome may be **recovery, disability or death**.
- Host may become a clinical case, subclinical case or carrier
- **Secondary and tertiary levels of prevention** are possible
- **Screening** of disease may improve prognosis and increase survival.

LEVELS OF PREVENTION

Primordial Prevention

- **Prevention of emergence of risk factors** in communities or populations in which **they have not yet appeared**

- **Harmful lifestyles** are discouraged - through individual and mass education
- Useful in **prevention of chronic disease**; it is **primary prevention** in its purest sense

Primary Prevention

- Prevent disease occurrence by **action taken prior to the onset of disease** (in **pre pathogenesis phase**).
- **Health Promotion**: Health education (most cost effective intervention); Lifestyle & behavioral change; Nutritional intervention (food fortification); Environmental (safe water/housing).
- **Specific Protection+**: Immunization/Vaccination; vitamin A prophylaxis in children; Chemoprophylaxis; Protection against occupational hazard, accidents, allergens

Secondary Prevention

- Action to **interrupt progress of disease & its complications** by the two below measures
- **Early diagnosis**: (screening test, case finding e.g. Pap smear for Ca Cervix)
- **Treatment** (e.g. treatment of TB, leprosy, STD)
- **Health programmes initiated by the govt.** are usually at the level of secondary prevention
- **Mass treatment** approach is used in secondary prevention, in control of certain diseases (e.g. **trachoma, malaria, yaws, pinta, bejel**)

Tertiary Prevention

- Intervention in **late pathogenesis phase**
- Includes **Disability limitation, Rehabilitation**.

Event	Classification	Interpretation
Accident	Disease (intrinsic pathology)	Affects functioning of a person
Loss of lower limb	Impairment (anatomic or functional abnormality)	Loss of anatomical structure (leg)
Cannot walk	Disability (Activity restriction)	Normal daily essential activity like walking is affected
Unemployed	Handicap (Psychosocial disadvantage)	Loses his job; cannot actively fulfill his role for the family and society

SOURCE AND RESERVOIR

- **Source**: of infection is defined as "the person animal object or substance from which an infectious agent passes or is disseminated to the host".
- **Reservoir**: is defined as "any person, animal, arthropod soil or substance (or combination of these) in which an infectious agent lives and multiplies, on which it depends primarily for survival and where it reproduces itself in such a manner that it can be transmitted to susceptible host". (In short the reservoir is the natural habitat in which the organism metabolizes and replicates.).
- The terms **reservoir and source** are **NOT** always synonymous as seen in table below:

Infection	Source	Reservoir
Hookworm	Soil	Man
Tetanus	Soil	Soil
Typhoid	Feces contaminated food/water	Man (Cases/ carriers)

HOST

- A person or animal that affords subsistence to the infectious agent under natural conditions.
- **Primary host**: **Definitive host**; the host in which the parasite passes its sexual stage.
- **Secondary host**: **Intermediate host**; the host in which the parasite passes its asexual stage.
- **Obligate host** means the only host e.g. man in measles and typhoid fever
- **Transport host**: A carrier in whom the organism remains alive but does not undergo development
- **Paratenic host**: similar to intermediate host BUT it is not needed for the parasite's development to progress (a "dumping ground" for non-mature stages of the parasite which can accumulate in high numbers).
- **Dead-end host**: An intermediate host that does NOT allow transmission to the definitive host - thereby preventing the parasite from completing its development (e.g.: humans are dead-end hosts for *Echinococcus*).

CARRIERS

- An infected person or animal that **harbors an infectious agent** in the absence of discernible clinical disease and serves as a potential source of infection for others.

Incubatory carrier	Those who shed the infectious agent during incubation period of the disease, e.g. measles, mumps, polio, pertussis, hepatitis B, Influenza, diphtheria. (m ² p ² hidl)
---------------------------	--

Contd...

Contd

Convalescent carriers	Those who shed the disease agent during the period of convalescence, e.g. cholera, diphtheria, dysentery, pertussis, typhoid fever . ("Cold Dip causes Diseases of Particular Type")
Healthy carriers	They are victims of subclinical infection who have developed carrier state without suffering from overt disease, e.g. cholera, polio, diphtheria, meningococcal meningitis, typhoid. " Chol-Poi-Dip-Ti(y) p-Men! "
Pseudo-carriers	Carriers of avirulent organisms are called pseudo-carriers

ZOONOSIS

An infection or infectious agent transmissible under normal conditions from **vertebrate animals to man**

Anthropozoonosis

- Infection transmitted to man from vertebrate animals e.g. **rabies, plague, hydatid, anthrax, trichinosis**.

Zoo-anthroposis

- Infection transmitted from man to vertebrate animals e.g. human TB in cattle.

Amphixenosis

- Infection maintained in both man and lower vertebrate animals that may be transmitted in either direction. e.g. *Leishmania* and *S. japonicum*.

DEFINITIONS

Infection: The entry and development or multiplication of infectious agent in the body of man or animals.

Contamination: The presence of an infectious agent on the body surface; also on or in clothing, beddings, toys etc. Contamination of a body does not imply a carrier state.

Pollution: is the presence of offensive but not necessarily infectious matter in the environment.

Infestation: The lodgement, development and reproduction of arthropods on the surface of the body or in the clothing e.g. lice, itch mite.

Contagious disease: Transmitted through **contact** e.g. scabies, leprosy, trachoma, STDs

Exotic: disease **imported into a country** in which they do not otherwise occur e.g. rabies in UK

Epizootic: an outbreak of disease in a **bird population**

Enzootic: an **endemic occurring in animals**

EPIDEMICS

- The '**unusual**' occurrence in a community or region of a disease/specific health-related behavior (smoking) or other health related events (traffic accidents) in excess of expected occurrence are called epidemic.
- An arbitrary limit of two standard errors from the endemic frequency is used to define the epidemic threshold for common diseases.
- The first step in conducting an epidemic investigation is to **verify the diagnosis**.

Point source epidemic

- A.k.a **Common source / Single exposure** epidemics
- The resultant cases all develop within **one incubation period** of the disease (e.g. in an epidemic of food poisoning).
- The epidemic tends to be **explosive with clustering of cases** within a **narrow interval of time**; the **epidemic curve rises and falls rapidly** with NO secondary waves (Ex: **Bhopal gas tragedy, Minamata disease in Japan**).

Continuous Epidemic

- **Multiple/repeated exposure** epidemic
- E.g. **Gonorrhea**, a well of contaminated water, **Legionnaire's disease**.

Propagated Epidemic

- Usually of **infectious origin** (polio, hepatitis A); **person to person** transmission occurs; also via **arthropods/animal reservoir**.
- **High secondary attack rate** occurs.
- **Cases occur later than known length** of incubation period.
- **Slow transmission** occurs in areas with good herd immunity.

ENDEMIC

Refers to the constant presence of a disease or infectious agent within a given geographic area.

Hyper-endemic The disease is constantly present at a high incidence and/or prevalence rate and affects all age groups equally.

Hyper-endemic Means a high level of infection beginning in early in life and affecting **most of the child population**.

Sporadic Cases occur irregularly, haphazardly from time to time and generally infrequently.

Pandemic An epidemic affecting a large portion of the population occurring over an entire nation or continent e.g. **influenza, cholera** etc.

“PERIODS/TIMES”

Incubation period	Time interval between entry of infectious agent and the first sign or symptom of the disease in question.
Median incubation period	Time required for 50% of cases to occur following exposure .
Latent period	Used for non-infectious diseases and is the time interval from ' disease initiation to disease detection '.
Serial interval	Time interval between the onset of primary case and secondary case .
Generation time	Time interval between the receipt of infection by a host and maximal infectivity of the host .
Lead time	Is the advantage gained by screening , i.e. the period between diagnosis by early detection and diagnosis by other means .
Secondary attack rate	The number of exposed persons developing the disease within the range of the incubation period, following exposure to the primary case.

Secondary Attack Rates

• Chickenpox	90%
• Whooping cough	90%
• Mumps	86%
• Measles	80%
• Smallpox	40%

Quarantine

- **Healthy individual isolated** (kept under observation) after exposure to disease for longest incubation period of that disease. Ex: **6 days for yellow fever**.
- In contrast to isolation, quarantine applies to restrictions on healthy contacts of infectious disease.
- Quarantine literally means “**40 days!**”

	Isolation	Quarantine
Separation of	Cases	Healthy contact of cases
Done for	Cases themselves	Other persons around
Level of prevention	Secondary (treatment)	Primary (specific protection)
Duration	Till recovery (period of communicability)	Till maximum incubation period

Surveillance

- Surveillance is collection and analysis of data for action. It is of 3 types:

- **Passive** - when data/reports are sent by designated health facilities or individual on their own, periodically as routine.
➤ *Example:* A patient with fever coming on his own to the PHC, Dispensary, Private Practitioner or Hospital.
- **Active** - When designated official and usually external to the health facility visits periodically and seeks to collect data from individuals or registers, log books, medical records and facility to ensure that no reported data are missing/incomplete.
➤ *Example:* Health worker goes house to house every fortnight to detect fever cases, collect blood slides (under malaria component of National Vector Borne Disease Control Program).
- **Sentinel:** Monitoring of rate of occurrence of specific conditions to assess the stability or change in health levels of population, it is also the study of disease rates in a specific population to estimate trends in larger population
- Helps in 'identifying missing cases' and 'supplementing notified cases'
- Sentinel Surveillance is done in National AIDS Control Program wherein STD clinics, ANC Clinics are sentinel sites to monitor trends

Monitoring Versus Surveillance

Monitoring	Surveillance
Performance and analysis of routine measurements aimed at detecting changes in environment or health status of a population	Continuous scrutiny of the factors that determine the occurrence and distribution of disease and other conditions of ill-health
One Time linear activity	Continuous Cycle
No feedback present	Feedback present
No inbuilt action component present	Inbuilt action component present
Stops once disease is eliminated/eradicated	Continues even after disease is eliminated/ eradicated
Smaller concept	Broader concept

INCUBATION PERIODS

Short IP (< 7 days)	Medium IP (7-21 days)	Long IP (> 21 days)
• Influenza: 8 to 72 h	• Trachoma: 5 to 12 d	• Hepatitis A: 15 to 45 d
• Cholera: 1 to 2 d	• Whooping cough (pertussis): 7 to 14 d	• Hepatitis B: 45 to 180 d
• Anthrax: 1 to 3 d		• Ascariasis: about 2 months
• Bacillary dysentery: 1 to 7 d		

Contd..

Contd.

Short IP (< 7 days)	Medium IP (7-21 days)	Long IP (> 21 days)
• Diphtheria: 2 to 6 d	• Polio: 7 to 14 days (3 to 35 d)	• Malaria: 3 weeks
• Pneumonic plague: 1 to 3 d	• Measles: 10 d	• Filariasis: 8-16 months
• Bubonic plague: 2 to 7 d	• Typhoid: 10 to 14 d (3 d to 3 weeks)	• TB: Months – years
• Yellow fever: 3 to 6 d	• Chickenpox: 14 to 16 d	• Leprosy: Months – years
• Meningococcal meningitis: 3 to 4 d	• Rubella: 2 to 3 weeks (18 d)	
• Kyasanur forest disease: 3 to 8 d	• Mumps: 2 to 3 weeks (18 d)	

Periods of Infectivity

Disease	Infectious period
Chickenpox	5 days before rash to 6 days after last crop
Diphtheria	2-3 weeks (shorter with antibiotic therapy)
Mumps	3 days before salivary swelling to 7 days after
Rubella	7 days before onset of rash to 4 days after
Measles	From onset of prodromal symptoms to 4 days after onset of rash
Scarlet fever	10-21 days after onset of rash (shortened to 1 day by penicillin)
Whooping cough	7 days after exposure to 3 wks after onset of symptoms (shortened to about 7 days by antibiotics)

PERIODIC FLUCTUATION IN DISEASES

Seasonal Trend

- Measles, varicella, cerebrospinal meningitis, upper respiratory infections, malaria etc.
- **Non-infectious** diseases may exhibit seasonal variation e.g. **sunstroke, hay fever, snake bite**

Cyclic Trend

- Measles, rubella, influenza; **automobile accidents** in some countries are frequent on weekends.
- Occur due to naturally occurring antigenic variations in the level of **herd immunity (antigenic variations)**.

Secular Trend

- Changes in the occurrence of disease over a **long period**; e.g. coronary heart disease; DM, Lung cancer; TB, Polio, Typhoid.

BIOLOGICAL TRANSMISSION

Propagative	The agent merely Propagates (multiplies) in vector, but no change in form, e.g. Plague bacilli in rat fleas.
Cyclo-Propagative	The agent Changes in form and Propagates (e.g. Malarial parasite in mosquito. “ CPM ” (remember CPM tablet in wards!))
Cyclo -develop-mental	The agent undergoes only Development but NO multiplication, e.g. Dracunculiasis , microfilaria in mosquito.

INSECT-BORNE DISEASES

Arthropod-Borne Diseases

Arthropod	Diseases transmitted
Mosquito	See below
Housefly	Typoid and paratyphoid fever, diarrhea, dysentery, cholera, gastro-enteritis, amoebiasis, helminthic infestations, poliomyelitis, conjunctivitis, trachoma, anthrax, yaws, etc.
Sandfly	Kala-azar, oriental sore, sandfly fever, oroya fever.
• tSetSe fly	Sleeping Sickness
Louse	Epidemic typhus, relapsing fever, trench fever (“ Lousy Epidemics always Relapse in Trenches!! ”)
Rat flea	Bubonic plague , endemic typhus, chiggerosis, hymenolepis diminuta
Blackfly	Onchocerciasis
Reduviid bug	Chagas disease
Hard tick	Tick typhus, viral encephalitis, viral fevers, viral hemorrhagic fever, (e.g., Kyasanur forest disease), tularemia, tick paralysis, human babesiosis
Soft tick	Q fever, relapsing fever
Trombiculid mite	Scrub typhus, Rickettsial-pox
Itch-mite	Scabies
Cyclops	Guinea-worm disease, fish tapeworm (D.latum)
Cockroaches	Enteric pathogens



Fig. 14.1: Louse

Mosquito-Borne Diseases

Type of mosquito	Disease
Anopheles	Malaria
Culex	Bancroftian filariasis Japanese encephalitis (Culex vishnui in south India) West Nile fever Viral arthritis (Epidemic polyarthritis)
Aedes	Chikungunya, Chikungunya hemorrhagic fever Dengue, Dengue hemorrhagic fever Rift valley fever Filaria (not in India) Yellow fever (not in India)
Mansonoides	Malayan (Brugian) filariasis Chikungunya fever

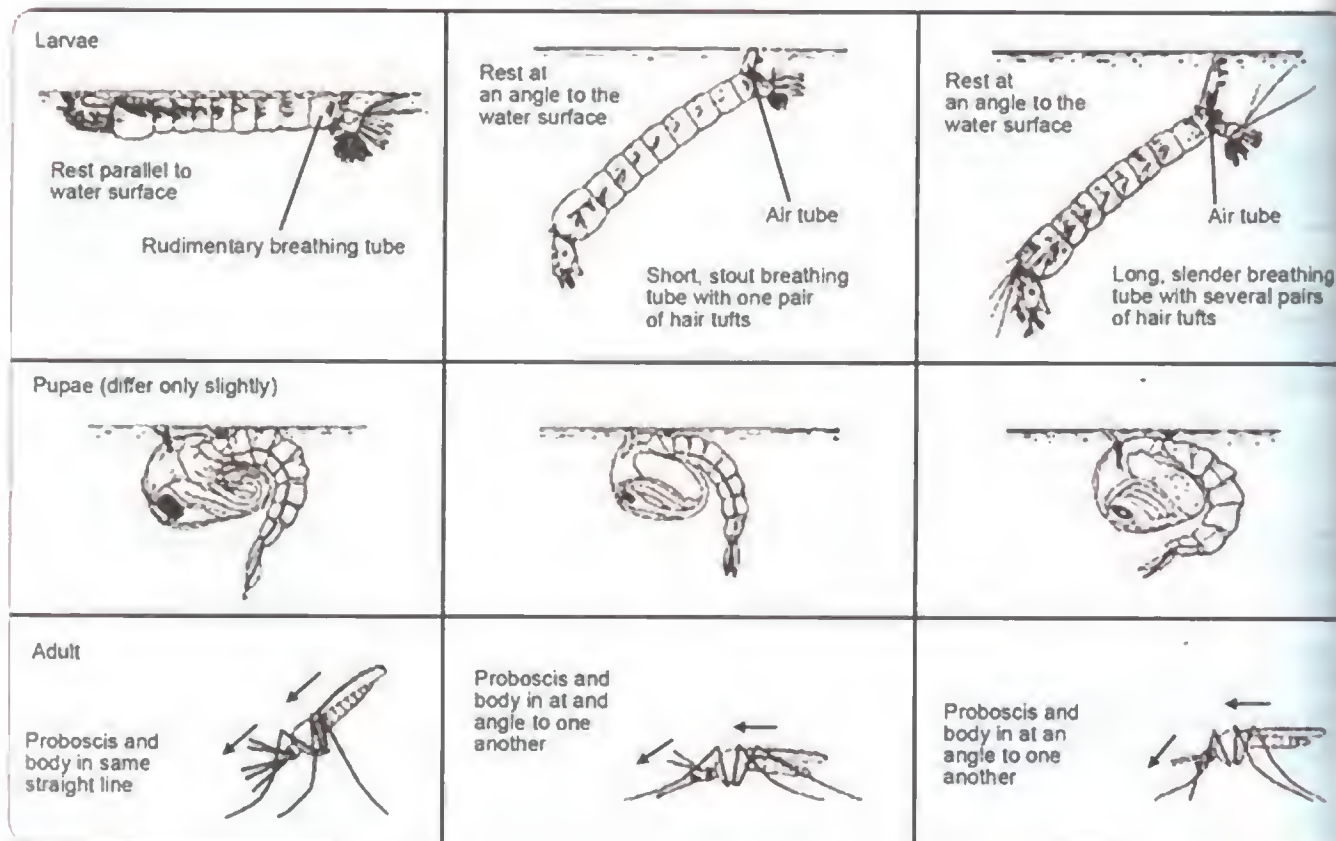


Fig. 14.2: Different types of mosquitoes



Fig. 14.3: Anopheles

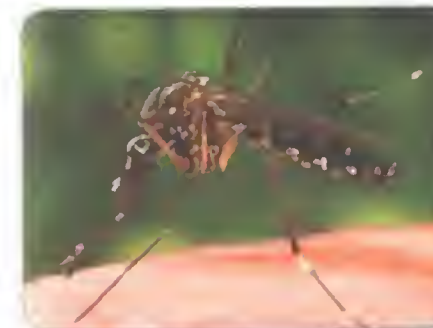


Fig. 14.4: Aedes

Classification of Mosquito Control Measures

Anti-larval measures	<ul style="list-style-type: none"> Environmental control Chemical control: Mineral oils, Paris green, Synthetic insecticides Biological control
Anti-adult measures	<ul style="list-style-type: none"> Residual sprays Space sprays Genetic control
Protection against mosquito bites	<ul style="list-style-type: none"> Mosquito net Screening Repellants

Areas of Distribution of Female Anopheles Mosquito

Plains	A. culicifacies, A. philippinensis
Coastal regions	A. stephensi, A. sundanicus
Foot-hill regions	A. fluviatilis, A. minimus
Urban areas	A. stephensi
Rural areas	A. culicifacies

CONCEPTS OF CONTROL OF DISEASE

- Disease control:** Is reducing the transmission of disease agent to such a low level that it ceases to be a public health problem. It aims at reducing:

- Incidence of the disease
- Duration of the disease
- Effects of infection
- Financial burden to the community

- Disease elimination:** Is complete interruption of transmission of disease in a defined geographical area, but the causative organism may be persisting in environment. Disease elimination is a 'geographical term', i.e. can be used only for a country or a region. India has eliminated 3 diseases till date:

- **Guinea worm** (Dracunculiasis): February 2000
- **Leprosy:** December 2005 (Elimination criterion: <1/10,000)
- **Yaws:** Sep 2006
- Next disease likely to be eliminated from India: Polio myelitis, Neonatal tetanus, Kala azar, Lymphatic filariasis

- Disease eradication:** Is complete 'extermination' of organism

- Is 'tearing out by roots' of a disease
- Exhibits 'All or none phenomenon'
- Disease eradication is a 'global term', i.e. can be used only for whole planet
- World has eradicated ONLY 1 disease till date: **Smallpox** (declared eradicated on 8 May, 1980)
- Diseases that are amenable to eradication are **measles, diphtheria, polio and guinea worm**

ALL ABOUT TUBERCULOSIS

Epidemiology Indices for TB

- Incidence of TB Infection** (Annual infection rate, Annual risk of infection, ARI): Percentage of population under study who will be newly infected with TB among non-infected in 1 year:

- Expresses **attacking force of TB** in community
- In developing countries 1% ARI corresponds to: 50 SS +ve cases per 1000, 000 population
- **Tuberculin conversion index** is the 'best indicator' for evaluation of TB problem and its trend in the community

- Prevalence of TB infection:** Percentage of individuals who show a positive reaction to standard tuberculin test

- **Tuberculin test** is the 'only way' of estimating the prevalence of infection in a population
- Represents cumulative experience of population in recent as well as remote infection with TB

- Incidence of disease:** Percentage of new TB cases per 1000 population:

- Reveals trend of problem, including impact of control measures

- Is of utility only in countries where high proportion of new cases are detected and notification is reliable
- **Sputum smear** examination (AFB) is a reliable method of estimation
- **Prevalence of disease or case rate:** Percentage of individuals whose sputum is positive for TB bacilli on microscopic examination:
 - 'Best available practical index to estimate case load' in community
 - Age specific prevalence is most relevant index.
- **Prevalence of suspect cases:** Is based on X ray examination of chest:
 - NO epidemiological significance is attached to this index
- **Prevalence of drug-resistant cases:**
 - Is directly related to chemotherapy
- **Mortality rate:**
 - Was earlier used as index of magnitude of TB problem
- **Tuberculosis control means reduction in the prevalence and incidence of disease in the community:**
 - The WHO defines that tuberculosis control should be achieved when the prevalence of natural infection in the group of ages 0-14 years is of the order of 1%. This is about 40% in India.

Tuberculin/PPD

- **Discovered by Von Pirquet (1907)**
- **Tuberculin:** Purified protein derivative (PPD) has replaced the antigen old tuberculin (OT); Tuberculin's have also been prepared from atypical mycobacterium: PPD-Y
- **PPD is a purer preparation, gives fewer non-specific reactions and is easier to standardize:**
 - Standard PPD (PPD-S) contains: 50,000 tuberculin units (TU) per mg [1 TU = 0.00002 mg PPD]
 - WHO advocates 'PPD-RT-23 with Tween 80'.
- **Dosage:** First Strength (1TU), Intermediate strength (5TU), Second strength (250TU)
- **Tuberculin test conversion** is defined as an increase of 10 mm or more within a 2-year period, regardless of age
- **Tuberculin test in use:**
 - **Mantoux** intradermal test: more precise test of tuberculin sensitivity
 - **Heaf** test: Quick, easy, reliable and cheap, preferred for testing large groups
 - **Time multiple puncture** test unreliable, NOT recommended
- **Tuberculin test is the 'only way of estimating the prevalence of infection in a population'**

- **Tuberculin test has lost its sensitivity as an indicator of the true prevalence of infection, in countries with high coverage of BCG.** (True prevalence rates are exaggerated by infection with atypical mycobacteria and boosting effect of a second dose of tuberculin).

Mantoux Test

- **Dose:** 1 TU of PPD in 0.1 ml injected intradermally on forearm
- **WHO advocated preparation:** PPD-RT-23 with Tween 80
- **Is a test of prognostic significance**
- **Has limited validity due to lack of specificity**
- **Readings: Result read after 72 hrs (3d)**
- **Only induration is measured:**
 - Induration > 9 mm: **Positive** (Past or current infection with TB)
 - Induration 6-9 mm: **Doubtful** (M. tuberculosis or Atypical mycobacteria)
 - Induration < 6 mm: **Negative**.

False Mantoux Reactions

False +ve Mantoux	False -ve Mantoux
Faulty technique of injection	Pre-allergic phase
Using degraded tuberculin	High fever
Too deep injection	Measles and chicken pox
Infection of other mycobacterium	Whooping cough
Repeated tuberculin testing	Malnutrition
Prior BCG vaccine	HIV/AIDS
	Use of anti-allergic drugs
	Use of immunosuppressants

Sputum Microscopy and Culture

- **Sputum smear examination (Z-N staining) by direct microscopy:** is the 'method of choice as a case finding tool for tuberculosis'
- **Sputum culture examination:** is offered as a centralized service at district and regional chest clinic laboratories:
 - Only meant for chest symptomatic who are smear negative
 - Useful for carrying out sensitivity tests and monitoring drug treatment.

Mass Miniature Radiography (MMR)

- **Is NOT used now as a case-finding tool**
- **Only useful:**
 - As an additional criterion for diagnosis of Pulmonary TB, when one sputum smear is positive out of two

- To exclude bronchiectasis/aspergilloma in frequent/severe positive sputum smear cases
- In suspected complication in a breathless patient needing specific treatment (e.g. pneumothorax, pericardial effusion, pleural effusion)

STOP TB Strategy

- **Vision:** A world free of TB; launched in 2006 by WHO.
- **Goal:** to dramatically reduce the global burden of TB by 2015, in line with Millennium Development Goals and STOP TB partnership targets.

The End TB Strategy (2016-2020)

- **Vision:** A world free of TB (Zero deaths, disease and suffering due to TB)
- **Goal:** End the global tuberculosis epidemic

Latent Tuberculosis (Latent TB)

- **Description:** Latent tuberculosis is where a patient is infected with *Mycobacterium tuberculosis*, but does not have active tuberculosis disease:
 - Latent TB are NOT infectious
- **Main risk:** 10% will go on to develop active TB at a later stage in life
- **Tests used to identify patients with latent TB:**
 - Tuberculin skin tests (Mantoux test, Heaf test, Tine test)
 - Alpha-interferon tests.
- **To give treatment for latent TB to someone with active TB is a serious error: TB will not be adequately treated and there is a serious risk of developing drug-resistant strains of TB.**

Drug Susceptibility Testing

- **Line Probe Assay (LPA).**
- **Cartridge Based - Nucleic Acid Amplification Test (CBNAAT), Xpert MTB/RIF** testing using the Gene-Xpert platform.

Drug Resistance in TB

- **Primary (Pre-treatment) resistance:** Resistance shown by the bacteria in a patient, who has not received the drug in question before.
- **Secondary (acquired) resistance:** Here, the bacteria were sensitive to the drug at the beginning of treatment, but became resistant during the course of treatment with it.
- **Mono-drug resistance:** Resistance to at least one first-line drug.
- **Poly-drug resistance:** Resistance to more than one first-line anti-TB drug (other than both INH and Rifampicin)

MDR-TB (Multi Drug Resistant TB)	XDR-TB (Extensively Drug Resistant TB)
<ul style="list-style-type: none"> • At least resistant to both INH AND Rifampicin • Now DOTS PLUS is used for MDR-TB 	MDR-TB + Resistant to fluoroquinolone + Resistant to one or more of these second line injectable drugs (amikacin, capreomycin, kanamycin)

Sputum Disinfection Methods in Tuberculosis

- Cresol (methylphenol) and other alcohols
- Autoclaving at 121 deg.C for 15 mins.
- Boiling at 100 deg.C for 20 mins.
- Vapor formaldehyde and Liquid formalin.
- Ethylene oxide
- Sodium hypochlorite
- Glutaraldehyde
- Carbolic acid
- **NOTE:** Chlorhexidine is inactive against MTB.

Revised National TB Control Program (RNTCP)

- **Directly Observed Treatment, Short Course (DOTS)** strategy was launched formally as Revised National TB Control Programme in India in 1997.
- DOTS is the **most effective strategy** available for controlling TB.
- **DOTS Plus** strategy is for appropriate management of Multi Drug Resistant TB (MDR TB).
- **NRI** = National Reference Laboratory, 6 in number:
 - National TB Institute, Bangalore
 - National Institute for Research in TB, Chennai
 - Lalaram Swarup Institute of TB and respiratory disease, Delhi
 - IALMA Institute, Agra
 - Regional Medical Research Centre, Bhubaneswar
 - Bhopal Memorial Hospital and Research Centre, Bhopal
- **IRL** = Intermediate Reference Laboratory
- **DMC** = District Microscopy centre; **most peripheral lab** under the RNTCP - serves a population of 1 lakh (50,000 in hilly/tribal areas)
- DOTS is given by peripheral health staff such as MPW's, Dais, Anganwadi workers, Teachers, ex-patients etc. They are known as **DOT agent** and paid incentive/honorarium of ₹150 per patient completing the treatment.

INTCP endorsed TB diagnostics

- ▶ **Smear for AFB**
 - **Z-N stain** or **Fluorescent stains** with direct/indirect microscopy with/without LED light.
- ▶ **Culture:**
 - Solid (L-J medium) or Liquid (Middle Brook) using manual semi-automatic or automatic machines.
- ▶ **Rapid diagnostic molecular test:**
 - **PCR based Line Probe** assay for MTB OR
 - **Real time PCR based Nucleic Acid Amplification test** (NAAT) for MTB complex (ex: GeneXpert).

Serological Tests for TB

- Serological tests for TB has been **banned by the Govt of India** in 2012.

Nikshay

- **NIKSHAY** is the platform for the National Tuberculosis Programme Surveillance System.
- TB surveillance using case based internet based IT system
- Launched in **May 2012**.
- Derived from two Hindi words! (NI= 'nivarani' and KSHAY = 'tuberculosis') — meaning "**eradication of TB**".
- **e-NIKSHAY** will gradually replace the paper-based system of recording and reporting and mobile/web applications, tablets and call centres on real-time basis will be used.
- The **Nikshay-Anshadhi**, the Centre for Development of Advanced Computing (C-DAC)'s **web - based TB drug supply management system** is a major step towards adapting technology to improve supply chain management of TB drugs

IGRA

- IGRA (Interferon gamma Release Assay) is used for **diagnosis of latent TB** infection.
- They are surrogate markers of M.tuberculosis infection and indicate a **cellular immune response** to M.tuberculosis.
- They **CANNOT** distinguish between latent TB and active TB infection and **CANNOT** be used for diagnosis of active TB (**which is a microbiological diagnosis**).
- However, IGRA is **NOT** affected by BCG vaccination status (especially in countries like India where BCG is given at birth).
- Examples are "QuantIFERON- Gold in Tube" test and "T-Spot TB" test.

- Antigens used are: ESAT6, CFP10, TB7.7 of Mycobacterium tuberculosis.
- **Very useful in vaccinated population**—as it is not affected by vaccinees like that of tuberculin test

Treatment Categories in DOTS

Category of Treatment	Type of Patient	Regimen
New cases	New sputum smear +ve	2(HRZE) ₁
Category I	New sputum smear -ve	+
Red Box	New extra-pulmonary	4(HR) ₁
	New others	
Previously Treated	Sputum smear +ve Relapse	2(HRZES) ₁
Category II	Sputum smear +ve Failure	+
Blue Box	Sputum smear +ve treatment after default	1(HRZE) ₁
	Others	+
		5(HRE) ₁

- Number before the letters refers to the number of months of treatment. The subscript after the letter refers to the number of doses per week. H (Isoniazid) 600 mg; R (Rifampicin) 400 mg; Z (pyrazinamide) 1500 mg; E (Ethambutol) 1200 mg; S (streptomycin) 750 mg. Patients who weigh more than 60 kg receive additional rifampicin 150 mg. Patients more than 50 years receive streptomycin 500 mg.
- Examples of **seriously ill extrapulmonary TB** = TB spine, TB meningitis; TB peritonitis; TB pericarditis; intestinal TB; genitourinary TB; TB pleurisy.

RNTCP Regimen for MDR-TB

- **Intensive phase (6-9 months):** 6 drugs (Pyrazinamide, Kanamycin, Levofloxacin Ethionamide, Ethambutol and Cycloserine) "PK-LEEC".
- **Continuation phase (18 months):** 4 drugs (Levofloxacin, Ethionamide, Ethambutol and Cycloserine) "LEEC".
- New drug for MDR TB (approved under RNTCP) **Bedaquiline fumarate** is approved USFDA for use as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR TB) when an effective treatment regimen cannot otherwise be provided.

RNTCP Regimen for XDR-TB

- **Intensive Phase (6-12 months):** 7 drugs (Capreomycin, PAS, Moxifloxacin, Amoxiclav, Linezolid, High dose INH, and Clofazimine). "CPM ALICE"
- **Continuation Phase (18 months):** 6 drugs (PAS, Moxifloxacin, Amoxycrav, Linezolid, High dose INH, and Clofazimine) "PM ALICE"

- **Delamanid** is another new Anti-TB drug that is WHO approved for adults with MDR TB, BUT the process for introduction under RNTCP is still ongoing (not yet approved under RNTCP).

More TB-related High Yield Points

- Country with **highest TB burden** in world: India
- In 1993 the **World Health Organization (WHO)** declared tuberculosis a **global emergency**.
- Under RNTCP, the currently recommended dose of **INH for chemoprophylaxis is 10 mg/kg** (instead of currently recommended dosage of 5 mg/kg) administered daily for 6 months.
- **PMDT: Programmatic Management of Drug resistant Tuberculosis.**

Automated Culture Systems

- Newer methods of cultivation of MTB.
- **MGIT (BACTEC)** – Automated **Mycobacteria Growth Indicator Tube** – medium used in this system is **7H9 Middle brook medium** with fluorometric detection based on oxygen consumption by the micro organism for its growth
- **MGIT also detects resistance to Pyrazinamide** – because this is added in the medium
- Another system used is ESP system – recently this helps to detect **drug susceptibility of mycobacteria** also.

Xpert MTB/RIF assay

- ▶ Molecular rapid test method for diagnosis of pulmonary and **extra pulmonary TB** — WHO recommended diagnostic tool
- ▶ Principle – Real time PCR; Cartridge based assay
- ▶ Time period to diagnose – less than 2 hours
- ▶ Helps to identify rifampicin resistance also

National Strategic Plan (NSP) 2017–2025

- The **NSP for TB elimination 2017-25** is a framework to guide the activities of all stakeholders including the national and state governments, development partners, civil society organizations, international agencies, research institutions, private sector, and many others whose work is relevant to TB elimination in India.
- **VISION: TB-free India** with zero deaths, disease and poverty due to tuberculosis.
- **GOAL:** To achieve a rapid decline in burden of TB, morbidity and mortality while working towards **elimination of TB in India by 2025**.

INDEX-TB Guidelines

- **INDEX-TB Guidelines** are guidelines for **extra pulmonary TB**. They include:
 - ▶ **X-pert MTB/RIF assay** maybe used as adjunct in diagnosis of lymph node TB and TB meningitis but NOT pleural TB.
 - ▶ **Steroids** maybe used in HIV negative patients with **TB meningitis** (for 4 weeks) and **TB pericarditis** but NOT pleural TB.
 - ▶ **Duration of ATT:** For **TB meningitis** – **9 months**; For lymph node and abdominal TB – **6 months**.

WORM INFESTATIONS**Guinea worm (Dracunculiasis)**

- Caused by *Dracunculus medinensis* (nematode)
- Last Guinea worm case in India July 1996 (Jodhpur, Rajasthan)
- India certified for Elimination of Guinea worm (WHO): Feb 2000
- India certified **Guinea worm disease free: Feb 2001**
- **Water** based disease (Cyclops play a role in transmission)
- Reservoir: an infected person (no animal reservoir)
- Guinea worm shows **cyclodevelopmental** transmission
- Mode of transmission: **Consumption of water containing Cyclops** harboring infective stage of parasite
- Treatment of cases: Nidazole, Mebendazole and Metronidazole
- No drug is effective for preventing disease transmission
- No drug is suitable for mass treatment

Hookworm (Ancylostomiasis)

- Causative agent: *Ancylostoma duodenale*; *Necator americanus*
- Reservoir of infection: Man
- Mode of transmission: Direct penetrating of skin of foot and by oral route
- Incubation period:
 - ▶ 5 weeks: 9 months (*A. duodenale*)
 - ▶ 7 weeks (*Necator americanus*)
- Hook worm infection is a.k.a: **miners anemia, tunnel disease, brickmaker's anemia, Egyptian chlorosis**
- Average blood loss in hook worm infection: **0.03-0.2 ml/worm/day**
- Hook worm infection is a/w: **Iron Deficiency Anemia/Hypoalbuminemia**

- **Cutaneous larva migrans:** a skin disease caused by the larvae of various nematode parasites, the MC of which is *Ancylostoma braziliense*
- **Endemic Index (Chandlers Index):** It is average no of hook worm eggs per gram of faeces for the 'entire community'.
- Interpretation of CI: **Kato-katz Technique** is employed

Average no. of eggs/gm stools	Interpretation
< 200	Not much significance
200-250	Potential danger
250-300	Minor public health problem
> 300	Important public health problem

LATEST DATA

Term	Values
Population of India	1210 million or 1.21 billion (2011 census) 1320 million or 1.32 billion (2017)
Annual Growth Rate	1.64% (2011 census) 1.2% (2017)
Population density	382/sq.km (2011 census) 445/sq.km (2016)
Sex ratio in India	933 Females/1000 Males (2011 census)
Literacy rate	74.04 (M = 82, F = 65) - 2011
Life expectancy at birth	Males = 64; Females = 67 (2011) Males = 66.9; Females = 69.9 (2017)
Total Fertility Rate	2.2 (2015-16)
Crude Birth rate	20 (2012)
Crude Death rate	7 (2015)

POPULATION

Stages of Demographic Cycle, By Prof. CP Blaker

High stationary	BR = CDR (so population remains stationary); India before 1920; AGR = 0
Early expanding	BR unchanged, CDR; South Asian & African countries; AGR > 1
Late expanding	BR, ↓ CDR; (births exceed deaths, so still population is expanding); China, Singapore; India has entered this phase now; AGR = 2
Low stationary	BR, ↓↓ CDR (Zero population growth); Austria, UK, Denmark; AGR = 0
Declining	BR < CDR; (Diminishing population); Germany, Hungary; AGR is negative

Key: BR = Birth Rate; DR = Death Rate; AGR = Annual Growth Rate

- However, **Thompson, Bogue and Notestein** believed that there are only three stages of population available in the world - pre-transition stage, transition stage and post transition stage as below.
 - Pre transition stage = Blaker's First stage (**high stationary**).
 - Transition stage
 - Early Transition = Blaker's Second stage (**early expanding**)
 - Mid Transition = Blaker's Third stage (**late expanding**) - **India** falls into this phase.
 - Late Transition = Blaker's Fourth stage (**low stationary**)
 - Post-transition stage = Blaker's Fifth stage (**low stationary**)

EXTRA EDGE

- The historical analyses of **Thomas McKeown** attributed the modern rise in the world population from the 1700s to the present to **broad economic and social changes rather than to targeted public health or medical interventions!!**
- According to UN, the world population - reached **7 billion in 2011**; will reach **8 billion by 2025**; **9 billion by 2037** and **11 billion by 2100**.

Couples

- An "**eligible couple**" refers to a currently married couple wherein the wife is in the reproductive age (15-45 years). There will be at least 150-180 such couples for 1000 population in India.
- "**Target couple**": include families with one child and even newly married couples with a view to develop the acceptance of family planning from the earliest stage.

WATER

Chlorination

Bleaching powder	When freshly prepared it contains 33% of available chlorine . (most effective & cheapest way disinfecting well)
Chlorine solution	4 kg of bleaching powder with 25% available chlorine is mixed with 20 L of water, it will give 5% of solution
Prerequisites for chlorination	<ul style="list-style-type: none"> • Water should be clear and free from turbidity • Chlorine demand of water should be estimated • Contact period should be at least 1 hour.
"Break point" chlorination	The point at which the residual chlorine appears in water. Minimum concentration of free chlorine required is 0.5 mg/l for 1 hour .
Superchlorination	Done for heavily polluted water whose quality fluctuates greatly.
Disinfecting action of chlorine	Best as a disinfectant when pH of water is 7 and is mainly due to hypochlorous acid and hypochlorite ion.
Orthotolidine (OT) Test	Enables both free and residual chlorine in water to be determined.
OT- arsenite test	Determines free chlorine and combined chlorine separately . Horrock's apparatus is used to estimate chlorine demand of water.
High test hypochlorite	Also called perchloron has 60-70% available chlorine
Chlorine tablets	A single tab of 0.5g is sufficient to disinfect 20 L of water
Chlorine gas	First choice for disinfecting large body of water
Iodine	Used for emergency disinfection of water . 2 drops 2% ethanol solution of iodine for contact period of 20-30 minutes; Potassium Permanganate - not used now
Boiling of water	Satisfactory method for household water ; "rolling boil" for 5-10 minutes . No residual protection offered.

Hardness of Water

Temporary hardness	Due to Bicarbonates of Calcium and Magnesium.
Permanent hardness	Due to Calcium and Magnesium sulfates, chlorides, nitrates
Permutit process	(Base exchange methods) & addition of Na₂CO₃ removes both temp. & permanent hardness
Nalgonda Technique	Defluoridation of water is done by using phosphates

Classification of Hard Water (as mg/l of CaCO₃)

Classification	Level of hardness (mEq/L)
Soft	0 - 50 mg/L (Less than 1)
Moderately hard	51 - 150 mg/L (1-3)
Hard	151 - 300 mg/L (3-6)
Very hard	> 300 mg/L (over 6)

Classification of Drinking Water according to Bacteriological Tests

	Presumptive coliform count per 100 ml	E.coli count per 100 ml
Class I Excellent	0	0
Class II Satisfactory	1- 3	0
Class III Suspicious	4 - 10	0
Class IV Unsatisfactory	More than 10	0.1 or more

WASTE AND SEWAGE

Wastes

Sewage	Waste water + excreta
Sullage	Waste water not containing excreta (ex. From kitchen, bathroom)

Contd.

- **UP has largest population.**
- India's age pyramid constitutes children & population of pre-reproductive age mainly **Broad base & tapering top**.
- **Kerala has highest literacy rate (93)** and Bihar has lowest (63).
- India is **second most populous** country (after China)
- The year 1921 is called the year of "great divide".

Contd...

Scum	After primary sedimentation of sewage, organic matter settles down and <i>sludge & fatty layer which floats</i> is called scum
Dry weather flow	Average amount of sewage which flows through the sewerage system in 24 hrs

Biological Oxygen Demand (BOD)

- Indicator of **organic content of sewage/strength of sewage**
- Defined as the amount of oxygen absorbed by a sample of sewage during specified period (**5 days**)

at a specified temperature, generally 20 deg.C for the aerobic destruction or use of organic matter by living organisms.

- If **BOD > 300 mg/L** and above, sewage is **strong** and if it is < 300 mg/L is said to be weak.

Water Pollution

- Presumptive Coliform count:** No sample should contain E.coli in 100 ml for public distribution. Total number of coliforms that are permitted is 3/100 ml.
- Fecal streptococci, Saline, Nitrate, Ammonia: indicates **recent fecal pollution of water**
- Cl. perfringens:** indicates **remote (past)** fecal pollution of water.

VACCINES**National Immunization Schedule, India (NIS) for infants, children and Pregnant women**

Vaccine	When to give	Dose	Route	Site
For Pregnant Women				
TT-1	Early in pregnancy	0.5 ml	Intra-muscular	Upper Arm
TT-2	4 weeks after TT-1*	0.5 ml	Intra-muscular	Upper Arm
TT-Booster	If received 2 TT doses in a pregnancy within the last 3 years*	0.5 ml	Intra-muscular	Upper Arm
For Infants				
BCG	At birth or as early as possible till one year of age	0.1 ml (0.05 ml until 1 month age)	Intra-dermal	Left Upper Arm
Hepatitis β-Birth dose	At birth or as early as possible within 24 hours	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
OPV-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks (OPV can be given till 5 years of age)	2 drops	Oral	Oral
Pentavalent 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks (can be given till one year of age)	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Rotavirus [†]	At 6 weeks, 10 weeks and 14 weeks (can be given till one year of age)	5 drops	Oral	Oral
IPV	Two fractional dose at 6 and 14 weeks of age	0.1 ml	Intra-dermal two fractional dose	Intra-dermal: Right upper arm
Measles/MR 1 st Dose [‡]	9 completed months-12 months (can be given till 5 years of age)	0.5 ml	Sub-cutaneous	Right upper Arm
JE-1 ^{**}	9 completed months-12 months.	0.5 ml	Sub-cutaneous	Left upper Arm
Vitamin A (1 st Dose)	At 9 completed months with measles-Rubella	1 ml (1 lakh IU)	Oral	Oral

Contd...

Contd...

Vaccine	When to give	Dose	Route	Site
For Children				
DPT booster-1	16-24 months	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Measles MR 2 nd dose [‡]	16-24 months	0.5 ml	Sub-cutaneous	Right upper Arm
OPV Booster	16-24 months	2 drops	Oral	Oral
JE-2	16-24 months	0.5 ml	Sub-cutaneous	Left Upper Arm
Vitamin A ^{***} (2 nd to 9 th dose)	16-18 months. Then one dose every 6 months up to the age of 5 years	2 ml (2 lakh IU)	Oral	Oral
DPT Booster-2	5-6 years	0.5 ml	Intra-muscular	Upper Arm
TT	10 years & 16 years	0.5 ml	Intra-muscular	Upper Arm

*Give TT-2 or Booster doses before 36 weeks of pregnancy. However, give these even if more than 36 weeks have passed. Give TT to a woman in labor, if she has not previously received TT.

**JE Vaccine is introduced in select endemic districts after the campaign.

***The 2nd to 9th doses of Vitamin A can be administered to children 1-5 years old during biannual rounds, in collaboration with ICDS.

†Phased introduction, at present in Andhra Pradesh, Haryana, Himachal Pradesh and Orissa from 2016 & expanded in Madhya Pradesh, Assam, Rajasthan, and Tripura in February 2017 and planned in Tamil Nadu & Uttar Pradesh in 2017.

‡Phased introduction, at present in five states namely Karnataka, Tamil Nadu, Goa, Lakshadweep and Puducherry. (As of Feb' 2017)

EXTRA EDGE

- Under NIS; JE Vaccine **only in 181 endemic districts** in select states
- Under HIS; HiB introduced as Pentavalent vaccine – HiB + HepB + DPT[†] in 18 states.

Latest Update on Polio Vaccines

- From April 2016, **Bivalent OPV** is used in India (containing type 1 and type 3 strains) **instead of trivalent OPV**.
- Govt. of India re-introduced one dose of **Injectable Polio vaccine (IPV)** under National immunization program from November 2015. This one dose of IPV (0.5 ml) was given IM along with third dose of OPV at 1-4 weeks.
- But currently, IPV has been launched as **two-dose fractional (0.2 ml) intradermal** schedule at **6 & 14 Weeks**. (since WHO reports that two fractional doses produce better immunogenicity rather than single IM dose!)

"Use Within " Time for Reconstituted Vaccines

- BCG = 3 hours
- Measles = 1 hour
- Varicella, Yellow fever = 30 minutes
- JE vaccine = 2 hours

Live attenuated vaccines

- **Bacterial:** BCG, Typhoid oral
- **Viral:** OPV, Yellow fever, Measles, Mumps, Rubella, Chicken Pox, Influenza
- **Rickettsial:** Epi.typhus
- **Contraindications for LAV's:** Immunodeficiency, pregnancy, whole body radiation.
- **Give SubCutaneous only:** MMR, Varicella, JE, Yellow fever
- **DO NOT Freeze:** "T" vaccines (DPT, DT, TT), BCG, Hepatitis B, HiB and diluents
- **Store in Freezer:** OPV (**most heat sensitive**), measles

Contraindications/Precautions with/to Immunization

- Live vaccines are CI in pregnancy
- Live vaccines are CI in immunodeficiency
- Vaccine CI in asymptomatic HIV: None
- Vaccine CI in symptomatic HIV: All live vaccines **except measles and BCG**.
- Vaccination after administration of immunoglobulin's is CI for at least 3 months.
- Vaccines contraindicated in ARTI/ diarrhea: NONE
- Vaccines contraindicated together: **Yellow fever and Cholera vaccine**

- Vaccine contraindicated in *progressive neurological disease*; *Pertussis* vaccine
- Inactivated (killed) vaccines are CI if there has been significant reaction to previous dose-toxicogenic reaction.
- Hay fever, sickle cell anemia and TB are relative contraindications sometimes.
- **Egg allergy** is a contraindication to immunization with *Influenza or yellow fever* vaccine.

Strains of Commonly Used Vaccines

Vaccine	Strain(s)
BCG	Danish-1331 strain (WHO recommended)
OPV/IPV	P1, P2, P3 strains (Monovalent or Trivalent)
Measles	Edmonston-Zagreb strain (MC) Schwartz strain Moraten strain
Mumps	Jeryl Lynn strain
Rubella	RA 27/3
Yellow fever	17 D strain
Varicella	OKA strain
Japanese Encephalitis	Nakayama strain Beijing P3 strain SA 14-14-2 (Used in India)
Swine Flu (killed)	A7/ California/ 2009
Malaria	SPf 66 strain (Lytic Cocktail) Pf 25 strain

BCG Vaccine (Bacille Calmette-Guérin)

- BCG is the **only vaccine** with **intra-dermal** route of administration
- After vaccination, a **papule** develops and reaches a size of 4-8 mm in about 5 weeks. It then breaks into a **shallow ulcer**, rarely open but usually seen **covered with a crust**. **Healing** occurs spontaneously within **6 to 12 weeks** leaving a **permanent tiny, round scar**, 4-8 mm in diameter.
- **Mantoux positivity starts after 8 weeks** has elapsed but sometimes about 1-4 weeks are needed.

DPT Vaccine (Diphtheria, Pertussis, Tetanus)

- **Pertussis component** in DPT vaccine enhances the **potency** of diphtheria toxoid.
- **Absorption** is carried out on a mineral carrier like **aluminium phosphate** or hydroxide.

- When issued to sub-centre the vaccine should be **used within a week**, the vaccine will lose potency **if kept at room temperature** over a longer period of time.
- DPT vaccine (all vaccines containing mineral carriers/adjuvants) should be given **deep IM** in the **upper and outer quadrant** of the **gluteal region**. For infants under 1 year, DPT should be administered in the **lateral aspect of thigh**.
- **Absolute contraindications** to **pertussis** vaccine are: **anaphylactic** reaction; **progressive** neurological disorder; **Encephalopathy** occurring within 7 days of vaccine.

Measles Vaccine

- **Measles vaccine**: a **live attenuated, tissue-culture vaccine** presented as a **frozen dried product**.
- Strains: **Edmonston-Zagreb** (MC); Schwarz, Moraten
- Each dose of 0.5 ml contains >1000 viral infective units of vaccine strain.
- Vaccine may also contain sorbitol and hydrolyzed gelatin as stabilizers and small amount of neomycin BUT NOT thiomersal.
- After reconstitution vaccine must be stored in dark at 2-8 Deg C and used within 4 hours.
- WHO recommends immunization at **9 months** of age. **0.5 ml SC** injection, reconstituted vaccine should be kept on ice and **used within 1 hour**. 5-10 days after immunization, a mild 'measles' illness (fever and rash) may occur — self-limiting.
- Immunity develops **11-12 days** after vaccination and is possibly for life (one dose = **99% protection**)
- Susceptible contacts over the age of 9-12 months may be protected against measles with measles vaccine provided that this is **given within 3 days of exposure**.
- Measles vaccine can be combined with other live vaccines as MMR (Measles, Mumps, Rubella)
- **CI** are pregnant women, acute illness, deficient cell mediated immunity and immunocompromised states;
- Adverse effects: transient **thrombocytopenia**, Toxic shock syndrome
- Eradication of measles is possible if (a) an immunization coverage of at least 96% of children under 1 year of age is achieved and (b) cumulation in immunity gap can be prevented.

EXTRA EDGE

- Measles vaccine can be and SHOULD be given to HIV positive children and adults and can be given as early as 6 months after birth of baby.
- WHO Measles elimination strategy: "**catch up, keep up, follow-up**".

Yellow Fever Vaccine

- Sensitivity of the lyophilised **17D vaccine** to heat is **major drawback** to the use of this vaccine in mass campaigns in tropical countries.
- Vaccine is given **SCQ at the insertion of deltoid** in a **single dose of 0.5 ml irrespective of age**.
- Immunity appears to **begin on the 7th day** and **lasts for more than 35 years** and possibly for life.
- **Revaccination after 10 years** is recommended for international travel.
- **Cholera and yellow fever vaccines** together or within 3 weeks interfere with each other, so whenever possible they should be given **3 weeks or more apart**.
- Protective immunity is achieved only after 10 days of yellow fever vaccination and hence yellow fever vaccination certificate becomes **valid only after 10 days of vaccination**.
- All travellers who do not have proof of vaccination will be **quarantined for up to 6 days**.
- The **WHO** announced that as of 11 July 2016, existing and new Yellow Fever vaccination certificates are **valid for life**. (India has still not adopted this).

Japanese Encephalitis Vaccine

- The **Japanese encephalitis vaccine**, Live is a preparation of Japanese encephalitis **live attenuated virus strain (SA 14-4-2)**.
- It is a lyophilized vaccine that looks like a **light yellow powder**.
- It should be **reconstituted with phosphate buffered saline**.

Pulse Polio Immunization

- PPIs are when oral polio vaccine is given to **all children in the country on a single day**, regardless to previous immunization. PPI is carried out on 'national immunization days' (NIDs) every year in **December & January**.
- The 1st PPI started on 9th December **1995** targeting all children < 3 years but later on age group was increased to all children < 5 years.
- The dose of OPV during PPIs are extra doses which supplement, and do not replace the doses received during routine immunization services.
- A country will be declared polio free only when no new cases will be reported for 3 consecutive years.
- Vaccine vial monitor use in PPI started after 1998 for efficacy.

- As on **25th Feb 2012**, India was removed from the list of polio-endemic countries.

Vaccine-Associated Reactions

Vaccine	Reaction
BCG	Osteitis and Osteomyelitis Suppurative lymphadenitis Disseminated BCGosis
Measles	Toxic shock syndrome Transient thrombocytopenia (also with MMR) Febrile seizures Encephalopathy
DPT, Pertussis	Shock Seizures Encephalopathy Persistent (> 3 hours) inconsolable screaming Hypotonic hypo-responsive episode (HHE)
Varicella	Acute cerebellar ataxia Pneumonitis
Rotavirus	Intussusception
Gullian Barre Syndrome	Killed influenza vaccine
OPV (Sabin)	Vaccine associated paralysis
Hypersensitivity	Hepatitis-B, Meningococcal vaccine, DPT, dT, MMR

Vaccine Vial Monitors (VVMs)

	Inner square lighter than outer circle. If the expiry date has not been passed, USE the vaccine
	At a later time, inner square still lighter than outer circle. If the expiry date has not been passed, USE the vaccine
	Discard point: Inner square matches colour of outer circle. DO NOT use the vaccine. Inform your supervisor
	Beyond the discard point: Inner square darker than outer circle. DO NOT use the vaccine. Inform your supervisor

Fig. 14.5: Vaccine vial monitors

- A VVM is a label containing a **heat-sensitive material** which is placed on vaccine vials to register cumulative heat exposure over time. With more heat inner square becomes darkened irreversibly.

More Vaccine Points

- The *first recombinant subunit vaccine* approved for use in humans (against hepatitis BQ) was made in yeast.
- Four new vaccines have been introduced into India's Universal Immunization Program (UIP), including injectable polio vaccine and an adult vaccine against Japanese encephalitis; vaccines against rotavirus, rubella.

RABIES (HYDROPHOBIA)**Basics of Rabies**

- Causative agent: *Lyssavirus Type 1* (Bullet shaped neurotropic RNA virus).
- Incubation period: variable [4 days to many years; ~ 3 to 8 weeks]
- Rabies is a **dead-end infection** in man
- Negri bodies** (Pathognomonic of Rabies): Intracytoplasmic eosinophilic inclusion bodies with basophilic granules in neurons
- Hydrophobia** is pathognomic
- Mode of transmission: Animal bites (dogs, cats, monkeys, cow, goat, sheep, buffalo, horses EXCEPT RAT BITE and HUMAN BITE); Licks (on abraded skin or abraded/unabraded mucosa); Aerosols (Rabies infected bats); Person to person (Rare but possible); Corneal and organ transplantation
- Rabies-free area**: No case of Rabies in man or animals for **past 2 years**
- Water is an Effective Natural Barrier against Rabies
- Rabies is NOT found in: Australia; China (Taiwan); Cyprus; Iceland; Ireland; Malta; Japan; New Zealand; Britain; Andaman and Nicobar islands (India); Lakshadweep (India).

Cold Chain Components (Equipment) and Levels in India

Level	Component	Temperature	Storage duration
State/Regional level	Walk In cold rooms (WIC)	+2°C to +8°C	3 months
	Walk in freezers (WIF)	-20°C to -40°C	
District level	Large ILRs (Ice lined refrigerator)	+2°C to +8°C	1 month
	Large DFs (Deep freezers)	-20°C to -40°C	
PHC level	Small ILRs	+2°C to +8°C	1 month
	Small DFs	-20°C to -40°C	
Sub-centre level	Vaccine carriers	+2°C to +8°C	48-72 hrs
	Day carriers	+2°C to +8°C	
Session level	Fully frozen icepack	+2°C to +8°C	1-3 hours

Types of Rabies Virus: Street Virus and Fixed Virus

Characteristic	Street Virus (SV)	Fixed Virus (FV)
Source	Naturally occurring cases	Serial brain passage of SV
Incubation period	20-60 days	4-6 days
Pathogenicity	For all mammals	Sometimes pathogenic
Negri Bodies	Formed	Not formed
Importance	Cause rabies	Used for vaccine preparation

Local Wound Treatment

- Cleansing**: Flush and wash wound area with plenty of **soap and running water** for minimum of **5-10 minutes**
- Suturing**: NOT recommended; if necessary, do 24-48 hours later
- Anti-rabies serum**: Local application with prior sensitivity testing
- Observe animal for **10 days**.

Type of Contact, Exposure and Recommended Post-Exposure Prophylaxis (PEP)

Category	Type of contact	Recommended PEP
I	Touching or feeding of animals Licks on intact skin Contact of intact skin with secretions/ excretions of rabid animal/ human case	None, if reliable case history is available
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Wound management Anti-rabies vaccine
III	Single or multiple transdermal bites or scratches, licks on broken skin Contamination of mucous membrane with saliva (i.e. licks)	Wound management Rabies immunoglobulin Anti-rabies vaccine

Vaccines for Rabies

Nervous tissue vaccines	Duck embryo vaccine (DEV)	Cell culture vaccines
<ul style="list-style-type: none"> Prepared from fixed virus grown in the brain of adult sheep (Simple type) or other animals. Crude products capable of causing severe/fatal reactions. Large number of doses are required. Suckling mouse brain vaccine: devoid of neuroparalytic effects. Govt. of India has STOPPED nervous tissue vaccine from 2004. 	<ul style="list-style-type: none"> Inactivated vaccine with reduced neuroparalytic effects. Allergy to egg proteins is a risk factor. Purified DEV available in India as VaxiRab. 	<ul style="list-style-type: none"> Human diploid cell culture vaccines – prepared in human diploid fibroblast cells; safe; highly potent; routinely used in India. "Second generation" tissue culture vaccines – derived from non-human sources based on either primary cell substrates (e.g. fetal, bovine kidney, chick embryo fibroblast, dog kidney cells, hamster kidney cells etc.) or non tumorigenic continuous cell lines (e.g. vero cells) Cheaper, potent, WHO recommended

New Recommended Regimens/Schedules

Type of prophylaxis	Regimen
POST EXPOSURE INTRAMUSCULAR	
Essen Regimen (1-1-1-1-1)	Day 0,3,7,14,28
POST EXPOSURE INTRADERMAL	
Updated Thai Red Cross Regimen (2 2 2 0-2)	Day 0, 3, 7,, 28
Post exposure in vaccinated individuals	Day 0, 3
Pre exposure prophylaxis	Day 0, 7, 21, 28

Other Management Guidelines

- Persons under antirabic treatment should avoid: Alcohol (during and 1 month after treatment); Undue physical and mental strain and late nights; Corticosteroids and other immunosuppressive agents
- Intramuscular injections of Cell Culture and Purified Duck Embryo Vaccines: **Deltoid** (not in buttocks)
- Volume of intradermal dose of Rabies Vaccine is 1/5th of intramuscular dose region, **lower quadrant of abdomen**
- Booster injections in Pre-exposure prophylaxis: at intervals of 2 years
- Most logical and cost effective approach for control of Urban Rabies: Elimination of stray dogs and swift mass immunization; At least 80% of entire dog population of the area must be immunized
- Anti Rabies Serum:
 - Horse Antirabies Serum: 40 IU/Kg on Day 0 (50% in Wound, 50% i.m)
 - Human Rabies Immunoglobulin: 20 IU/ kg (maximum in wound, rest i.m gluteal) (Concentration 150 IU/ mL)
 - Serum sickness with Horse Serum: 15-45%

MALARIA**Anopheles Mosquito**

There are over 55 species of anopheline mosquitoes in India:

- An. *Culicifacies*: Vector of **rural malaria**
- An. *stephensi*: Vector of **urban malaria**, breed in **overhead tanks**
- An. *Fluviatilis*: Efficient vector; highly anthropophilic, breed in **moving water**
- An. *Sundaicus*: Breed in **brackish water**

Epidemiology of Malaria in India

- Malaria season: MC in **July – November**
- June** is observed as **Anti-malaria month** in India since it is the **pre-monsoon season**.
- Definitive host: Female Anopheles mosquito
- Intermediate host: Man

Modes of Malaria Transmission

- Bite of female anopheline mosquitoes - Infective forms: sporozoites
- Injection of blood of a malaria patient containing asexual forms: Trophozoite induced malaria - seen in Transfusion malaria; Congenital malaria; Malaria in drug addicts
- Transfusion associated malaria** is transmitted by **trophozoites**; pre-erythrocytic schizogony is **absent**; relapses **do not** occur and incubation period is **short**.

Mosquito Vs Man

- Man and Anopheles mosquito compared as hosts involved in transmission of malaria

Man	Female anopheles mosquito
Secondary host	Primary host
Intermediate host	Definitive host
Asexual cycle	Sexual cycle
Schizogony	Sporogony

MEASUREMENT OF MALARIA

Pre-eradication era: Here the magnitude of the malaria problem in a community used to be determined mostly

from the reports of *clinically diagnosed malaria cases*. The classical malarimetric measures are given below. These *classical measures* may provide the needed information i.e., *the trend of the disease*.

Spleen rate	<ul style="list-style-type: none"> Percentage of children between 2-10 years showing enlargement of spleen. Adults are excluded since splenomegaly in adults maybe due to various other causes. The spleen rate is widely used for measuring the endemicity of malaria in a community.
Average enlarged spleen	<ul style="list-style-type: none"> Denotes average size of the enlarged spleen; a further refinement of the spleen rate.
Parasite rate	<ul style="list-style-type: none"> Percentage of children between 2-10 years showing malaria parasites in their blood films
Parasite density Index	<ul style="list-style-type: none"> Average degree of parasitemia in a well defined group of the population. Only the positive slides are included in the denominator
Infant parasite rate (IPR)	<ul style="list-style-type: none"> Percentage of infants below the age of 1 year showing malaria parasites in their blood films. Most sensitive index of recent malaria transmission in a locality. If the IPR is zero for 3 consecutive years in a locality, it is regarded as absence of malaria transmission, even though the Anopheline vectors may remain
Proportional case rate	<ul style="list-style-type: none"> Since the morbidity rate is difficult to determine except in conditions where the diagnosis and reporting of each case is carried to perfection, proportional case rate is used. Defined as the number of cases diagnosed as clinical malaria for every 100 patients attending the hospitals and dispensaries. This is a crude index since the cases are not related to the time/space distribution

Eradication era: Here, the *microscopic diagnosis of malaria* cases became the main method of diagnosis. These parameters are unlikely to reveal the true epidemiological picture unless the case detection machinery is fully supervised and very efficient. The parameters are:

Annual parasite incidence (API)	<ul style="list-style-type: none"> It is a sophisticated measure of malaria incidence in a community. It is based on intensive active and passive surveillance, and cases are confirmed by blood examination. API = confirmed cases during 1 year/population under surveillance X 1000.
Annual Blood Examination Rate (ABER)	<ul style="list-style-type: none"> ABER = No of slides examined/population X 100. The WHO expert committee on malaria in 1964 recommended that the monthly number of slides examined should be at least one percent of the population. In the modified plan of operation (MPO) the minimum prescribed is 10% of the population in a year. ABER is an index of operational efficiency
Annual falciparum incidence	<ul style="list-style-type: none"> Data are collected separately for total malaria cases and falciparum cases
Slide positivity rate and slide falciparum rate	<ul style="list-style-type: none"> Provide information on the trend of malaria transmission.

LYMPHATIC FILARIASIS

- Lymphatic Filariasis covers infection with 3 closely related nematode worms: *Wuchereria bancrofti*; *Brugia malayi*; *Brugia timori*
- Life cycle of parasite is **quite long (15 years or more)**
- Definitive Host: **Man**; Intermediate Host: **Mosquito**
- Vectors of Lymphatic filariasis:
 - Bancroftian Filariasis: *Culex* (C. fatigans/quinq-fascians in India), Anopheles, Aedes
 - Brugian filariasis: *Manosonia* (main in India), Anopheles, Coquillettidia

Stages of Filariasis

- Pre-Patent Period:** Time interval between inoculation of infective larvae and first appearance of detectable microfilariae (MF)
- Clinical incubation Period:** time interval between invasion of infective larvae to development of clinical manifestations- (8-16 months)
- Mosquito becomes infective:** When **third stage larvae migrates to Proboscis** of mosquito vector
- Asymptomatic amicrofilaraemia stage:** Absence of MF or clinical manifestations

Asymptomatic microfilaraemia: Blood positive for MF but **NO** clinical manifestations; acts as carriers and an important source of infection

Occult Filariasis (cryptic filariasis): No clinical manifestations or MF in blood; Due to a **hypersensitivity reaction** to filarial antigens; Ex: **Tropical pulmonary eosinophilia**.

Filaria Detection Tests

- MC method** used for **epidemiological assessment** of Lymphatic Filariasis (through **mass blood survey**): **Thick film** using 20 cu. mm of capillary blood (collected between 8.30 pm upto 12 midnight).
- Most sensitive method** of detecting low density micro-filaraemia: **Membrane Filter Concentration Method**.
- DEC Provocation test** (100 mg DEC oral): MF can be induced to appear in blood during daytime - Blood is examined 1 hour after DEC administration
- Good method** to detect low density microfilaraemia, when other methods fail: **Xenodiagnosis** - Mosquitoes allowed to feed on patients, then dissected 2 weeks later

EXTRA EDGE

- Chemotherapy of Filariasis: Diethylcarbamazine (DEC)**
- DEC medicated salt:**
 - Dose: 1-4 gm DEC/kg of salt for 6-9 months
 - Is a type of **Mass treatment** (using very low dose of drug)
- National filaria Control Programme (NFCP), 1955 is now a component of National Vector Borne Disease Control Programme (NVBDCP), 2003-04
- NVBDCP** covers Chikungunya, Dengue, Kala-azar, Lymphatic Filariasis, Japanese Encephalitis and Malaria.

JAPANESE ENCEPHALITIS

- Caused by **Group B arbovirus (Flavivirus)**
- Pigs** are '**Amplifier Hosts**': Pigs themselves do not manifest overt symptoms but circulate virus
- Cattle and buffaloes** are '**Mosquito attractants**': Infected but not the natural hosts of JE virus
- Horses** are **ONLY** domestic animals show signs of encephalitis due to JE virus
- Birds** are also involved in Natural History: Pond herons, cattle egrets, poultry and ducks
- Man** is an '**incidental Dead end Host**': Man to Man transmission is not seen. 85% cases occur in children < 15 years of age
- Vectors of JE: *Culex tritaeniorhynchus* (most important vector), *Culex vishnui* and *Culex gelidus*

- IP of JE in man; 5 - 15 days (9-12 days in mosquitoes)
- Case fatality rate: 20-40% may reach upto 58%
- In India: **Gorakhpur District of UP** contribute the largest no of cases
- 85% of cases of JE are reported in age below 15 years BUT JE is infrequent in infancy
- JE Vaccines are given below.

Vaccine	Strain
Mouse brain derived, purified & inactivated vaccine	Nakayama strain Beijing strain
Cell culture derived, inactivated vaccine	Beijing P3 strain
Cell culture derived, live attenuated vaccine	SA 14-14-2 Strain (in India)

FLEA INDICES IN M. PLAGUE

- Total flea index:** Is average no. of fleas of all species per rat
- Cheopis index:** Is average no of x. cheopis per rat; Is an indicator of potential explosiveness if outbreak occurs
- Specific percentage of fleas:** Percentage of different fleas
- Burrow Index:** Average no. of fleas per species per rodent burrow.

PREVENTION OF TETANUS IN WOUNDED

	Treatment by type of wound	
Immunity category	Wounds < 6 hours old, clean, non-penetrating, with negligible tissue damage	Other wounds
A	Nothing more required	Nothing more required
B	Toxoid 1 dose	Toxoid 1 dose
C	Toxoid 1 dose	Toxoid 1 dose + Human tetanus immunoglobulin
D	Toxoid complete course	Toxoid complete course + Human Tetanus Immunoglobulin

Where,

- A: Complete course of toxoid or booster dose in previous 5 years
- B: Complete course of toxoid or booster dose in previous 5-10 years
- C: complete course of toxoid or booster dose in > 10 years
- D: Has not had a complete course of toxoid or status is unknown.

- **True congenital glaucoma:** IOP rise occurs in **intrauterine life**.
- **Infantile glaucoma:** manifest after birth **until 3 years of age**.
- **Juvenile glaucoma:** manifest between **3-16 years of age**.

Etiopathogenesis

- **MC Boys, MC Bilateral**, most cases are **sporadic**, 10% are AR, chromosome 2.
- Pathology: **Trabeculodysgenesis, Barkan's membrane** (hypothetical membrane) covering angle of eye.

Clinically

- **Lacrimation, photophobia and blepharospasm;**
- **Hazy and Large cornea:** MC presenting symptom; **Corneal diameter more than 12 mm within the 1st year is always pathological.** (Corneal diameter at 6 months = 10 mm and at one year = 12 mm.)
- **Buphthalmos**—Ox eye (occurs only if age < 3 years).
- **Haab's striae** (Horizontal breaks in Descemet's membrane), increased IOP.
- **Progressive myopia** due to globe enlargement; subluxated lens, axial myopia, optic disc cupping
- **Causes of visual loss in PCG:** optic nerve disease, corneal scarring, anisometropic/strabismic amblyopia, myopic astigmatism, cataracts.

Treatment

- **Evaluation under anesthesia.** Measure Corneal diameter with calipers; IOP with Perkins hand held applanation tonometer. Gonioscopy with Koeppe gonioscopes; optic nerve evaluation, axial length measurement with ultrasound.
- Medical Rx: temporarily only; **AVOID brimonidine** since it causes apnea/hypotension, bradycardia/hypothermia in children < 6 years.

Definitive is **surgical** treatment—

- **Goniotomy:** An arcuate incision is made with a Barkan's goniotomy knife midway between the iris and Schwalbe's line.
- **Trabeculotomy:** A fine metal probe is passed into Schlemm's canal and is then swept into the anterior chamber thus exposing the Schlemm's canal directly to the aqueous humor.
- **Combined trabeculectomy with trabeculotomy** is now a days the **preferred procedure**.

EXTRA EDGE

- IOP maybe reduced minimally by: General anesthesia (esp. halothane); corneal edema and overventilation; IOP may **falsely increase with ketamine**, succinylcholine, endotracheal intubation, pressure from anesthetic mask, speculum use and inadequate ventilation.

D/D of cloudy cornea at birth

"STUMPED"—Sclerocornea, Trauma, Ulceration, Metabolic disorder (mucopolysaccharidosis, cystinosis), Peter's anomaly, Endothelial dystrophy (Congenital hereditary endothelial dystrophy, posterior polymorphous dystrophy), Dermoid.



Fig. 17.41: Congenital glaucoma

PRIMARY OPEN ANGLE GLAUCOMA

- A chronic slowly **progressive** neurodegenerative disease of optic nerve characterised by accelerated **ganglion cell death**, subsequent axonal loss and optic nerve damage and eventual field loss.
- Characterised by **adult onset**, IOP > 21 mmHg, **open angles**, **optic nerve damage** and no obvious systemic or ocular cause for raised IOP; previously called **chronic simple glaucoma**.
- Genetics: two genes — **myocilin (MYOC)**—earlier called **TIGR** (trabecular meshwork induced glucocorticoid response protein) on **chromosome 1q** and **optineurin gene on chromosome 10p**.
- **Etiology:** common in 5th and 6th decade; **multifactorial inheritance**; **family history** (siblings have greater risk than offsprings)

Ocular associations of POAG

High myopia,
Retinal vein Occlusion,
Retinal Detachment,
Retinitis Pigmentosa,
Fuch's endothelial dystrophy

Systemic associations of POAG

Diabetes mellitus, HTN,
Thyrotoxicosis,
CVS disease

- **Corticosteroid responsiveness**—POAG patient respond to chronic steroid therapy with a significant **increase in IOP**.
- Symptoms of POAG: **Painless progressive visual loss; mild eyeache or headache; visual field defect; frequent change of presbyopic glasses** (due to accommodative failure due to constant pressure on ciliary muscle and its nerve supply).
- Signs: **Visual acuity may remain good till late stage**, normal anterior segment with pupillary reaction normal until late stage; open angle on gonioscopy.
- **Asymmetry of the cup-disk ratio (> 0.2)** between the two eyes - you should suspect glaucoma.
- IOP changes: **Diurnal variation** recording may be necessary; A variation of IOP of over 5 mmHg is suspicious and **over 8 mmHg is diagnostic of glaucoma**, although the whole reading lies under limit of 21 mmHg. In late stages IOP is permanently raised over 21 mmHg.

Optic Disc Changes in Glaucoma

Early changes

- **Vertically oval cupping.**
- **Bayanetting sign.**
- Thinning of the neural rim (**ISNT rule** — normally Inferior rim thickest > Superior > Nasal > Temporal).
- **Nasal shifting** of disc blood vessels.
- **Splinter hemorrhages** at or near the disc margin — **Drance hemorrhage** (MC in **Normal Tension Glaucoma**).
- Atrophy of retinal nerve fibre layer (**RNFL defects**) that is seen with **red-free light** (green filter).

Advanced changes

- Total cupping seen as a white disc with loss of all neural rim and bending of retinal vessels at margin of disc also called **beaten pot cupping**.
- Openings of lamina cribrosa are visible upto margins of disc—**laminar dot sign**.

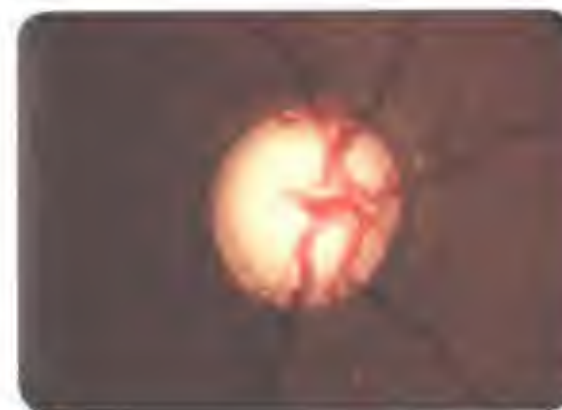


Fig. 17.42: Glaucomatous optic nerve

Visual Field Defects

- **Isopter contraction:** is the **earliest visual field defect in glaucoma** that refers to **mild generalized constriction of central as well as peripheral field**.
- **Baring of the blind spot:** means exclusion of the blind spot from the central field; also an early field defect.
- **Isolated paracentral scotoma:** earliest clinically significant field defect; may appear in the Bjerrum's area (an arcuate area extending above and below the blind spot to between 10° and 20° of fixation point).
- **Seidel scotoma:** with passage of time, paracentral scotoma joins blind spot to form a **sickle shaped Seidel scotoma**.
- **Bjerrum's or arcuate scotoma:** formed at a later stage by extension of Seidel scotoma in an area above or below the fixation point to reach the horizontal line. With further progression, a double arcuate scotoma (ring or annular) will develop.
- **Roenne's central nasal step:** It is created when two arcuate scotomas run in different arcs and meet to form a sharp right angled defect at the horizontal meridian.
- Generalized constriction of peripheral field along with **double arcuate scotoma** leads to **tubular vision**.
- Central vision is abolished and **lastly the temporal island of vision is also lost** with no perception of light.

Investigations in POAG

- **Goldmann Monocular (Kinetic) Perimetry** - replaced by automated/computerized perimeters now; still maybe useful in neurological lesions.
- **Automated standard white on white (static) Perimetry:** to detect visual field defects. **Humphrey** (most accepted) and; **Octopus perimetry** are used; **Stimulus size III MC (4 mm²)** used.
- **RNFL (Retinal Nerve Fibre Layer Analysis):** by **OCT** (Optical Coherence Tomography) OR **GDx VCC** (confocal scanning laser polarimetry) OR **HRT** (Heidelberg Retina Tomogram, confocal scanning laser ophthalmoscopy); (approximately 30-50% of optic nerve damage would have already occurred before defects become apparent on perimetry; hence **RNFL analysis is done to detect pre-perimetric glaucoma**).
- Water drinking **provocative test:** Patients drinks 1 litre of water following which IOP is recorded by applanation every 15 minutes for 1 hour. A rise of 8 mmHg is said to be significant - NOT routinely used now.
- Other **provocative tests NOT** in use now are **jugular vein compression, bulbar pressure test, priscot test, and caffeine test**.
- **DDLS** = Disc Damage Likelihood Scale

About ASHA

- ASHA must be a **resident of the village** – a woman (married/widow/divorced) preferably in the age group of **25 to 45 years** with formal education **upto 10th standard** having communication skills and leadership qualities.
- **One ASHA for 1000** population.
- In tribal, hilly and desert areas, **one ASHA per habitation**.
- NAMG = National Asha Mentoring Group

List of Drugs in ASHA Drug Kit

No.	Contents of Drug KIT
1.	DDK (Disposable Delivery Kit) for Clean deliveries at home
2.	Tab. Paracetamol
3.	Paracetamol syrup
4.	Tab. Iron Folic Acid (L)
5.	Tab. Punarvadu Mandur (ISM - Indian System of Medicine Preparation of Iron)
6.	Tab. Dicyclomine
7.	Tetracycline ointment
8.	Zinc Tablets
9.	Povidine Ointment Tube
10.	G.V. Paint (Gentian Violet)
11.	Cotrimoxazole syrup
12.	Paediatric Cotrimoxazole tablets
13.	ORS Packets
14.	Condoms
15.	Oral pills (In cycles)
16.	Spirit
17.	Soap
18.	Sterilized Cotton
19.	Bandages, 4 cm X 4 meters
20.	Nischay Kit (Pregnancy detection kit)
21.	Rapid Diagnostic Kit
22.	Slides for Malaria & Lancets
23.	Emergency Contraceptive Pill
24.	Sanitary napkins (to promote Menstrual Hygiene amongst adolescent girls)

List of Items in ASHA Equipment Kit

No.	List of Items in ASHA Equipment Kit
1.	Digital Wrist Watch
2.	Thermometer
3.	Weighing Scale (for newborn)
4.	Baby Blanket
5.	Baby Feeding spoon
6.	Kit Bag
7.	Communication Kit
8.	Mucous Extractor

Reproductive and Child Health (RCH) program

- Reproductive and Child Health-II (**RCH Phase II**) is a comprehensive programme **under the NRHM** commenced in **April 2005** with the main objective to bring about an improvement in mainly three critical health indicators i.e. **reducing total fertility rate, infant mortality rate and maternal mortality rate**.
- The target group of the programme is **women in the reproductive age group and children upto 5 years** of age.

IMNCI

- **IMCI** (Integrated Management of Neonatal and Childhood Illnesses) was a strategy designed by **WHO/UNICEF** inspired by the common observation that, in developing countries, illnesses strike as a group, rather than as a single disease - Ex: diarrhea and respiratory infection along with anemia and/or malnutrition.
- In India IMCI has been expanded to include neonatal care. Hence the "N" in **IMNCI**.
- IMNCI = Integrated Management of Neonatal and Childhood Illnesses is the key intervention **under RCH II**.
- **Pre-service IMNCI**
 - IMNCI is being included in the **curriculum of medical colleges** of the country.
- **Facility based IMNCI (F-IMNCI)**
 - The F-IMNCI training would provide the optimum skills needed by the **Medical officers and Staff Nurse at the FRU's** (First Referral Unit) - this thereby helps to address the acute shortage of Pediatricians in facilities.
 - It focusses on providing **appropriate inpatient management of the major causes of neonatal and childhood mortality** (such as asphyxia, sepsis, low birth weight, pneumonia, diarrhea, malaria, meningitis and severe malnutrition) in children at the FRU.
 - The master trainers at state and district level are **pediatricians from tertiary hospitals and medical colleges**.

Facility Based Newborn Care (FBNC)

- Setting up of facilities for care of Sick Newborn such as Special New Born Care Units (SNCUs), New Born Stabilization Units (NBSUs) and New Born Baby Corners (NBCCs) at different levels is a thrust area under NHM.

	Newborn Care Corner (NBCC)	Newborn Stabilisation Unit (NBSU)	Special Newborn Care Units (SNCUs)
Definition	A mandatory (compulsory) space within delivery room of all health facilities conducting deliveries to provide immediate care to all newborns at birth. (NBCC is present in all - PHC, CHC/FRU's and district hospitals also)	NBSU's are situated within or close proximity to the maternity ward where sick babies and LBW babies >1800 g can be cared for during short periods. All community health centres/first referral units (CHC/FRU) must have a NBSU in addition to NBCC.	SNCU is a neonatal unit which can provide specialised care (all care except assisted ventilation and major surgery) for all sick newborns and LBW infants < 1800 grams. All facilities conducting > 3000 deliveries/year should have SNCU. All district hospitals must have SNCU. (there will be a need of 5 SNCU of 12 beds for each district!)
Area and beds	20-30 sq. feet in size with 1 bed within labor room or operation theatre	4 beds with a total of 200 sq. feet area with 2 beds in postnatal ward for rooming in.	100 sq. feet required. (50 for patient care + 50 for ancillary area). Recommended number of beds is 12 beds/3000 deliveries with additional 4 beds/1000 more deliveries.
Equipment	Radiant warmer, weighing scale, foot operated pump suction, oxygen source, resuscitation bag with mask, laryngoscope, syringe hub cutter, wall clock and room thermometer.	High intensity phototherapy units, laryngoscope set and electronic baby weighing scale.	Oxygen supply with oxygen concentrator, pulse oximeter, electronic BP apparatus, multichannel monitor, ECG unit, mobile X-ray machine, transport incubator and electrical autoclave.
Service provided	Identification and prompt referral of at risk and sick newborns .	Management of hyperbilirubinemia and newborn sepsis ; Stabilisation and referral of sick newborns with very LBW.	All care (except assisted ventilation and major surgery) for all sick newborns and LBW infants < 1800 grams.
Training	Given for 2 days under Navjat Shishu Suraksha Karyakram (NSSK)	Given under F-IMNCI for 11 days for those not trained in IMNCI and 5 days for those already trained in IMNCI.	Given under FBNC; duration of training for SNCU's is 4 days of training + 2 weeks observership at SNCU.
Staffing	1 doctor; 1 nurse and 1 auxiliary midwife.	1 doctor and 4 nurses	3-4 doctors and 10 nurses

EXTRA EDGE

- In the **SNCU**, **Ancillary area** should have handwashing and gowning area, nursing station, clean area for mixing fluids and medications, doctors duty room, mother's area for breastmilk expression, unit store and a lab.

Home Based Newborn Care (HBNC)

- A new scheme has been launched to **incentivize ASHA** for providing Home Based Newborn Care.
- ASHA will make visits to all newborns according to specified schedule **up to 42 days** of life (**7 visits for home births** - on day 1, 3, 7, 14, 21, 28, 42; **6 visits only for facility births**, NO day 1 visit).
- The proposed incentive is **Rs. 50 per home visit** of around one hour duration, amounting to a total of **Rs. 250 for five visits**.
- This would be paid at one time **after 45 days of delivery**, subject to the following:

- recording of weight of the newborn in MCP card
- Ensuring BCG, 1st dose of OPV and DPT vaccination
- Both the mother and the newborn are safe till 42 days of the delivery, and
- Registration of birth has been done

EXTRA EDGE

- **Baby friendly hospital initiative** was launched by WHO/UNICEF in 1991 - it is a hospital that follows the WHO/UNICEF code of practice for **10 successful steps to breastfeeding**.

Mission Indradhanush

- **Mission Indradhanush** was launched by Ministry of Health and Family Welfare (**MOHFW**) in **2014**. (Indradhanush = **Rainbow**; the logo depicts seven colours of the rainbow).
- The objective of this mission is to ensure that **all children < 2 years as well as pregnant women are fully**

immunized with seven vaccine-preventable diseases namely:

- Diphtheria; Pertussis; Tetanus; Tuberculosis; Polio; Hepatitis B; Measles
- Mission Indradhanush aimed to fully immunize > 90% of newborns by 2020.
- **Intensified Mission Indradhanush (IMI)** has started since Oct 2017.
- The strategy of IMI is to cover all left outs and drop outs in select districts and urban areas with low routine immunization coverage in a specific time-frame (by December 2018).
- 4 rounds of immunization are proposed to be held for 7 days each month (from 7th to 13th of each month).

RMNCH+A

- **Reproductive, Maternal, Newborn, Child and Adolescent (RMNCH+A)** approach was launched in 2013 and it essentially looks to address the major causes of mortality among women and children as well as the delays in accessing and utilizing health care and services.
- It also introduces new initiatives like the use of **Score Card** to track the performance, **National Iron + Initiative** to address the issue of anemia across all age groups and the Comprehensive Screening and Early interventions for defects at birth, diseases and deficiencies among children and adolescents.

Navjat Shishu Suraksha Karyakram (NSSK)

- NSSK is a programme aimed to train **health personnel in basic newborn care and resuscitation**, has been launched to address care at birth issues i.e. Prevention of hypothermia and infection, Early initiation of Breast feeding and Basic Newborn Resuscitation.
- The objective of this new initiative is to have a trained health personal in Basic newborn care and resuscitation at every delivery point.
- The training is for **2 days** and is expected to reduce neonatal mortality significantly in the country.

India Newborn Action Plan (INAP)

- The India Newborn Action Plan (INAP) was launched in September 2014 with the aim of ending preventable newborn deaths and stillbirths by 2030.
- The goal of INAP is to attain **Single Digit Neonatal Mortality and Stillbirth Rates by 2030**.

Janani Shishu Suraksha Karyakram (JSSK)

- JSSK was launched on 1st June 2011 and has provision for both **pregnant women and sick new born till 30 days** after birth (in government hospitals) and includes:
 - **Free** and zero expense treatment; **Free** drugs and consumables; **Free** diagnostics & Diet; **Free** provision of blood; **Free** transport from home to health institutions; **Free** transport between facilities in case of referral; Drop back from institutions to home; Exemption from all kinds of user charges.
- The initiative would further **promote institutional delivery**, eliminate out of pocket expenses which act as a barrier to seeking institutional care for mothers and sick newborns and facilitate prompt referral through **free transport**.

Janani Suraksha Yojana

- The earlier **National maternity benefit scheme (NMBS)** has now been modified into a new scheme called JSY under the NRHM.
- It was launched on 12th April 2005 as a **100% centrally sponsored** scheme.
- Beneficiaries are **all women regardless of age and number of children** for delivery in government/private accredited health facilities or also at home.
- Eligibility for **Cash Assistance: BPL (Below Poverty Line) Certification** – This is required in all HPS states. However, where BPL cards have not yet been issued/updated or have not been updated, gram pradhan or ward member can certify the 'poor and needy' status of the expectant mother's family.
- The scheme focuses on the **poor pregnant woman with special focus for states having low institutional delivery rates**. States are classified on the basis of institutional delivery rate as:
 - **Low Performing States (LPS)**: states having **institutional delivery 25% or less**; LPS states includes **EAG** (Empowered Action Group) states and the states of **Assam & Jammu & Kashmir (10 states)**.
 - **High Performing States (HPS)**: States which have institutional delivery rate more than 25%; HPS includes all other states.
- **Disbursement of Cash Assistance**: As the cash assistance to the mother is mainly to meet the cost of delivery, it should be **disbursed effectively at the institution itself**.
- For pregnant women going to a public health institution (govt. hospital) for delivery, **entire cash entitlement**

should be disbursed to her in one go, at the health institution.

EXTRA EDGE

- In India, the eight **socioeconomically backward states** of Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Rajasthan, Uttaranchal and Uttar Pradesh, referred to as the **Empowered Action Group (EAG) states**, lag behind in the demographic transition and have the **highest infant mortality rates** in the country.

Other Important Programs

Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA)

- The PMSMA was introduced in 2016 to ensure quality **Antenatal care** pregnant women in the country.
- Under the campaign, a minimum package of antenatal care services would be provided to the beneficiaries on the **9th of every month** at the PMSMA Clinics to ensure that every pregnant woman receives at least **one checkup in the 2nd or 3rd trimester of pregnancy by a doctor (medical officer or OBGY specialist)**.
- It is recommended that irrespective of number of ante-natal care visits a ended by pregnant women, they should **attend at least one additional ante-natal care clinic** conducted as a part of PMSMA, during their second or third trimester.

DAKSHATA program

- Even though > 70% of deliveries in India now occur in institutions, there has not been a significant corresponding decrease in maternal and infant mortality rate.
- Hence the **DAKSHATA** program was launched with the goal of **"To improve the quality of maternal and newborn health care (MNH core) during the Intro- and immediate postpartum period, through providers who are competent and confident (Dakshata- meaning 'cleverness' or 'dexterity')"**.
- Training under DAKSHATA is given for **medical officers, nurses and ANMs** (Auxiliary Nurse Midwives)

LAQSHYA

- **Labour room Quality Improvement Initiative** started in 2017.
- To be introduced in **government medical college hospitals, district hospitals and high case load community health centres and subcentres**. The goals are
- **To improve Quality of care** during the delivery and immediate post-partum care.
- To enhance **patient satisfaction** and provide **Respectful Maternity Care (RMC)** to all pregnant women attending the public health facility.
- **To reduce maternal and newborn mortality & morbidity** (due to APH, PPH, retained placenta, preterm, preeclampsia / eclampsia, obstructed labour, puerperal sepsis, newborn asphyxia, and sepsis, etc)
- Expansion of **obstetric ICUs** at medical college hospitals and **obstetric HDUs** (High Dependency Units) at district hospitals and high load CHCs.

Rashtriya Bal Swasthya Karyakram (RBSK)

- RBSK is an important initiative aiming at early identification and early intervention for children **from birth to 18 years** to **cover 4 'D's** viz. **Defects** at birth, **Deficiencies**, **Diseases**, **Development** delays including disability.

Rashtriya Kishor Swasthya Karyakram (RKSK)

- RKSK was launched on 7th January 2014 in order to ensure holistic development of **adolescent** population.
- The programme includes all aspects of adolescent health in India - **sexual and reproductive health, nutrition, injuries and violence** (including **gender based violence**), **non-communicable diseases, mental health** and **substance misuse**.
- **Weekly Iron and Folic acid Supplementation (WIFS)** (100 mg elemental iron + 500 mcg folic acid) to reduce anemia in adolescents (**10-19 years**).
- **Menstrual hygiene scheme** for promotion of menstrual hygiene among **adolescent girls of 10-19 years** primarily in rural areas. A pack of 6 sanitary napkins (called '**Freedays**') for Rs. 6 will be distributed by the ASHA.

Village Health and Nutrition Day (VHND)

- The VHND is to be organized **once every month (preferably on Wednesdays)**, at the **AWC (Anganwadi Centre)** in the village itself - thus the villagers will not have to spend money or time on travel, health services will be provided at their doorstep.
- On the appointed day, ANM, ASHAs, AWWs, and others **should be present on time** - the villagers can interact freely with the health personnel and obtain basic health services and information on preventive and promotive aspects of health care

Intensified Diarrhoea Control Fortnight (IDCF)

- **Intensified Diarrhoea Control Fortnight (IDCF)** consist of a set of activities to be implemented in an intensified manner from (held usually in **June every year**) for prevention and control of deaths due to dehydration from diarrhoea across all States & UTs.
- IDCF has been held for **past 4 years** from 2014-2017. Its goals are:
 - To improve usage of **ORS and Zinc** for childhood diarrhoea.
 - To complement awareness activities (including Swachh) for prevention and management of diarrhoea in **under-five children**.

National Deworming Day (NDD)

- The NDD program has been launched in 2015 as WHO estimates that 220 million children below 14 years of age are at risk of Soil Transmitted Helminths (STH) infections in India.
- NDD program is organized **twice in a year** (February and August) covering all the **children from 1-19 years of age** except the States of Rajasthan and Madhya Pradesh (since STH prevalence in these two States is < 20%) where deworming is carried out once in a year.
- All the children are provided deworming tablet **Albendazole (free)** in schools and anganwadis

NATIONAL HEALTH POLICY

- The **National Health Policy- 2017** was approved by the Union Cabinet, Government of India on 16 March 2017. This is India's **third** National Health policy (NHP); earlier NHPs were released in 1983 and 2002.
- Salient Features are:
 - Shifting of focus from "sick-care" to "wellness", by **promoting prevention and well-being**.
 - Increasing **public health expenditure** to 2.5% of the GDP.
 - It proposes **free drugs, free diagnostics and free emergency and essential healthcare services in public hospitals**.
 - To focus on **primary health care** by allocating two-thirds (or more) of resources to primary care.
 - To reduce morbidity and preventable mortality of non-communicable diseases (NCDs) by advocating **pre-screening**.
 - To promote '**Make in India**' initiative by using drugs and devices manufactured in the country.
 - It highlights **AYUSH** as a tool for effective prevention and therapy that is safe and cost-effective. It proposes introducing **Yoga in more schools** and offices to promote good health.
 - Reforming **medical education**.

Key targets under the NHP-2017

- To **reduce**
 - **IMR** to 28 by 2019
 - **MMR** to 100 by 2020
 - **Neo-natal mortality rate** to 16 by 2025.
 - **Total fertility rate (TFR)** to 2.1 by 2025.
 - **Under Five Mortality** to 23 by 2025.
 - Premature mortality from **lifestyle disease** (CVS diseases, cancer, diabetes or chronic respiratory diseases) **by 25 %** by 2025.
- To **increase life expectancy** from 67.5 to 70 years by 2025.
- To **track DALY** for all diseases by 2022.
- NHP **2 beds per 1,000** of the population to enable access within the golden hour (the first 60 minutes after a traumatic injury). To **achieve the global 2020 HIV target** (also termed **90:90:90**; i.e. 90% of all people living with HIV know their HIV status, 90% of all people diagnosed with HIV infection receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression).

NATIONAL PROGRAMME FOR CONTROL OF BLINDNESS (NPCB)

- Launched in the year **1976** as a 100% centrally sponsored scheme with the goal of reducing the prevalence of blindness from 1.1% to 0.3%.

- NPCB output** is indicated by the **number of cataract surgeries** leading to **sight restoration**.

Trends of Blindness in India

Year of survey	Prevalence of blindness
2006-07	1.05%
Goal by 2010	0.5%
Goal by 2020	0.3%

Definition of Blindness

- The definition of Blindness under the NPCB has been **modified in 2017** to be in line with WHO Definition (1980). Both are the SAME now:
 - "**Presenting distance visual acuity less than 3/60(20/400) in the better eye and limitation of field of vision to less than 10 degrees from center of fixation**"
- The nomenclature of the scheme is also changed from 'National Programme for Control of Blindness' to '**National Programme for Control of Blindness and Visual Impairment**'

Low Vision

- Low Vision** (Visual acuity < 6/18-6/60): Is an important cause of sub-optimal visual functioning
- MC cause of Low Vision** in India is **Cataract**; Second MC is **Cataract Refractive Error**.

Vision 2020

- Vision 2020 - The Right To Sight:** A global initiative by WHO and International NGOs to reduce avoidable (preventable and curable) blindness by 2020
- Aim of Vision 2020:** To reduce the current projection of 75 million blind people by the year 2020 to a target of 25 million
- Vision 2020 is implemented as '4 five-year plans'** starting in 2000, 2005, 2010 and 2015 respectively
- Basic strategies Under Vision 2020:**
 - Disease preventing and control
 - Training of personnel
 - Strengthening the existing eye care infrastructure
 - Use of appropriate and affordable technology
 - Mobilization of resources
- The four tier structure under **Vision 2020** includes Centre of Excellence (20); Training centres (200); Service centres (2000) and Vision centres (20,000).

Global Vision 2020 (5 diseases)	India Vision 2020 (7 diseases)
Cataract	Cataract
Refractive errors and low vision	Refractive errors and low vision
Childhood blindness	Childhood blindness
Trachoma	Trachoma (Focal)
Onchocerciasis	Glaucoma
	Diabetes retinopathy
	Corneal blindness

NATIONAL AIDS CONTROL PROGRAM

- Launched in **1987**.
- Now **NACP -IV** going on (2012-2017).
- Group 1 states** = with > 5% **HIV infection** in high risk groups and > 1% in **antenatal women** = TN, AP, Karnataka, MP, Manipur and Nagaland.
- Group A districts** = > 1% antenatal clinic /parent to child transmission prevalence in a district at any time in the last 3 years
- HIV counseling and testing services include
- Integrated counseling and Testing centres (**ICTC**)
- Prevention of Parent to Child Transmission of HIV (**PPTCT**)
- HIV/TB collaborative activities
- From Dec 2013 **PPTCT includes** provision of **lifelong ART** (TDF + 3TC + EFV) to all pregnant and breastfeeding HIV women regardless of CD4 count and clinical stage of HIV progression.
- Case fatality rate** among **HIV infected TB** cases = 13-14% (4% in HIV negative)

HEALTH AGENCIES AND COMMITTEES

Bhare Committee, 1946

- Comprehensive proposal** for the development of a **national programme for health services** for the country.
- The committee observed "if the nation's health is to be built, the health programme should be developed on a foundation of preventive health work and that such activities should proceed side by side with those concerned with the treatment of patients"
- Integration of preventive & curative services.
- Establishment of PHC in 40,000 population in rural areas (short term measure).
- Setup of long term program (3 million plan)
- 3 months training in PSM for interns to prepare 'Social Physicians'.

Mudalliar Committee, 1962

- Advised **strengthening of existing PHCs** and also district hospitals.
- Each PHC should not serve > 40,000 population.
- Constitution of all India health services on the pattern of Indian administrative services.

Chadha Committee, 1963

- 'Vigilance' operations in respect to NMEP (malaria eradication).

Jungalwala Committee, 1967

- Defined **integrated health services**.

Mukerji Committee

- Mainly concerned with family planning program

Kartar Singh Committee 1973

- Committee for multipurpose worker (MPW) under health and family planning in place of ANM

Shrivastava Committee 1975

- Group on **medical education and support manpower**
- Recommended creation of paraprofessionals and semiprofessionals
- Development of '**Referral services complex**'.

- NACO has branded the **STI/RTI** (sexually transmitted infection/reproductive tract infections) services as "**Suraksha Clinic**".
- Red Ribbon clubs** are formed in colleges to give info and discuss about HIV infection.

NATIONAL IODINE DEFICIENCY DISORDERS CONTROL PROGRAM (NIDDCP)

- In 1992, the **National Goiter Control Programme** (NGCP) was renamed as the NIDDCP. Its objectives are:
 - Surveys to assess the magnitude of the Iodine Deficiency Disorders.
 - Supply of iodated salt in place of common salt.
 - Resurvey after every 5 years to assess the extent of Iodine Deficiency Disorders and the impact of iodated salt.
 - Laboratory monitoring of iodated salt and urinary iodine excretion.
 - Health education and Publicity.

NPCDCS PROGRAM

- National Program for Prevention and Control of Cancer, Diabetes, CVD and Stroke** (NPCDCS). This program has two components viz. (i) Cancer (ii) Diabetes, CVDs and Stroke.
- Main objective is to Prevent and control common NCDs through behaviour and **life style changes**.
- Global Action Plan** for the Prevention and Control of NCDs 2013-2020 - mainly cardiovascular diseases, cancers, chronic respiratory diseases and diabetes.
- It aims for a **25% reduction** of mortality from NCDs by 2025.

DISEASE RATES

Incidence

- Incidence is the **number of new cases** occurring in a defined population during a specified period of time. It is expressed as **per 1000 per year**. Incidence is a **rate**.
- Incidence is **NOT affected by the duration of disease**, the use of incidence is generally **restricted to acute conditions**.
- Special incidence rates** = **attack rate, secondary attack rate, hospital admission rate** etc.
- Incidence = (No. of new cases of a disease in a given time)/(total population).

Prevalence

- Prevalence refers specifically to **all current cases** (old and new) existing **at a given point in time or over a period of time** in a given population. **Prevalence is a ratio**
- Prevalence = Incidence C Disease Duration; P=I C D.**
- Prevalence = (# of existing cases of a given disease)/(total population).

- Prevalence > Incidence** for **chronic conditions**; longer the duration of the disease, the greater its prevalence. (e.g., TB, diabetes)
- Prevalence = Incidence** for **acute conditions** (e.g., common cold); If a disease has high mortality (i.e., rapid death) or easily curability (i.e., rapid recovery) it implies that the disease is acute and of a very short duration a prevalence will be low.

Case Fatality Rate (CFR)

- The percentage of individuals with a certain disease **who die within a certain amount of time**
- CFR = (people who die from a disease in a given time)/(# of cases during given time).

CONCEPTS IN SCREENING

Screening of Disease

- Screening test: Is used to search for an unrecognized diseases or defect, in apparently healthy individuals, by means of rapidly applied tests, examinations or other procedures. Difference between Screening versus Diagnosis is given below:

	Screening	Diagnosis
Done on	Apparent healthy	Cases (signs/symptoms)
Applied on	Groups, population	Individuals
Test results	Arbitrary & final	Not final, modifiable
Based on	One criterion (cut off)	Signs, symptoms, lab findings
Cost	Relatively cheaper	Expensive
Time taken	Relatively rapid	Time-consuming
Accuracy	Relatively inaccurate	Accurate
Basis of treatment	Cannot be used as basis	Useful basis for treatment
Initiative from	Investigator	Case with complaint

Some Important Screening Tests

Screening Test	Disease screened
Breast self examination	Breast cancer
Mammography	Breast cancer
Digital rectal examination (DRE)	Prostate cancer
Prostate specific antigen (PSA)	Prostate cancer
Papanicolaou (Pap) smear test, Visual inspection with 5% Acetic acid	Cervical cancer
Bimanual oral examination	Oral cancer
ELISA, RAPID, SIMPLE	HIV
Urine for sugar, Random blood sugar	Diabetes mellitus
AFP (alpha feto-protein)	Development anomalies in fetus
Fecal occult blood test	Colorectal cancer

Principles of Screening

WHO Criteria for Suitability of a Disease for Screening are:

- The disease should be an important health problem
- There should be an effective treatment available for the disease Facilities for diagnosis and treatment should be available
- There should be a latent or early asymptomatic stage of the disease
- There should be a test or examination for the diagnosis of disease
- The test should be acceptable to the population

- The natural history of the disease should be adequately understood
- There should be an agreed policy on who to treat
- The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole
- Case finding should be a continuous process, not just a 'once and for all' project.

Types of Screening

	Prescriptive screening	Prospective screening
Definition	People screened for own's benefit	People screened for others benefit
Essential purpose	Case detection	Disease control

	Prescriptive screening	Prospective screening
Request for screening	No specific request	Specific request from authority
Examples	Neonatal screening Pap smear Urine for sugar	Screening of immigrants HIV screening among sex workers

ANALYSIS OF DIAGNOSTIC TESTS

Test result	Disease	
	+	-
+	a (true positive)	b (false positive)
-	c (false negative)	d (true negative)

Sensitivity	Specificity
<p>The test's ability to detect all people with disease who truly have the disease (true positives) = $a / a + c \times 100 = 1 - \text{false negative rate}$</p> <p>Most acceptable screening tests are > 80% sensitive</p> <p>A false negative is a negative test in a patient with the disease!</p>	<p>The test's ability to correctly identify all people without disease, i.e., those who do not have the disease (true negatives) = $d / b + d \times 100 = 1 - \text{false positive rate}$</p> <p>Used as confirmatory test after a positive screening test</p> <p>Most acceptable confirmatory tests are > 85% specific</p> <p>Ex: HIV testing. Screen with ELISA (sensitive, high false positive rate, low threshold); confirm with Western blot (specific, high false negative rate, high threshold).</p>

Mnemonic: "SPIN" = SPecificity rules IN; "SNOUT" = SeNsitivity rules OUT.

Predictive Value

- Predictive value reflects the **diagnostic power** of the test. It **depends upon** sensitivity, specificity and disease prevalence.
- Positive Predictive value (PPV):**
 - Ability of a screening test to identify correctly all those who have the disease out of all those who test positive on the screening test (i.e. proportion of positive test results that are true positive)
 - PPV = $a / a + b \times 100$.**
 - PPV of a screening test is **directly proportional to the prevalence** of the disease — as the prevalence of the disease in the population increases, the PPV increases for the screening test.
- Negative Predictive value (NPV)**
 - Proportion of negative test results that are true negative i.e., the probability that a person with a negative test actually is disease free = $d / c + d \times 100$.

Relative Risk (RR, Risk Ratio)

- Relative probability of getting a disease in the exposed group compared to an unexposed group.

- $RR = [a/(a+b)]/[c/(c+d)]$
- A **RR > 1** suggests a **positive** relationship between the exposure and the disease (i.e., exposure increases the likelihood of developing the disease).
- A **RR < 1** suggests a **negative** relationship between the exposure and the disease (i.e., exposure decreases the likelihood of developing the disease).
- A **RR = 1** suggests **NO** relationship between the exposure and the disease.

Odds Ratio (OR)

- Odds of having disease in exposed group to odds of having disease in nonexposed group. Approximately equal to relative risk if prevalence of the disease is not too high.
- $OR = [a/c]/[b/d] = ad/bc$.

Attributable Risk

- The difference in the rates of a disease **between exposed and nonexposed populations**, or the proportion of disease occurrences that are **a result of the exposure** (e.g., smoking causes 1/3 of cases of pneumonia)

Absolute Risk Reduction

- The reduction in risk associated with a treatment as compared to a placebo.
- Number needed to treat (**NNT**) = 1/absolute risk reduction
- Number needed to harm (**NNH**) = 1/attributable risk.

Likelihood Ratio (LR)

- LR incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease.
- **LR or a positive test (LR+)** tells you how much the odds of the disease increase when the test is positive
➤ $LR+ = \text{Sensitivity} / (1 - \text{Specificity})$
- **LR or a negative test (LR-)** tells you how much the odds of the disease decrease when the test is negative
➤ $LR- = (1 - \text{sensitivity}) / \text{Specificity}$.

MORE TOPICS

Heat Stress Index (HSI)

- **HSI** represents the *percentage of heat storage capacity of an average man*.

HSI value	Interpretation
0	No thermal stress
10-30	Moderate to mild heat strain
40-60	Severe heat strain
70-90	Very Severe heat strain
100	Upper limit of heat tolerance

Headquarters

- UNESCO : Paris
- WHO : Geneva
- UNICEF : New York
- FAO : Rome
- World Bank : Washington, DC

Assisting Agencies

- SIDA: in TB + leprosy
- DANIDA: in *blindness control + leprosy*
- UNICEF: in GOBI campaign for breast feeding (**GOBI FFF** = Growth monitoring, Oral rehydration, Breast

feeding, Immunization, Female education, Family spacing and Female supplements)

- CARE: In *midday meal* program
- Ford foundation: In rural health and *family planning*
- **UNDP** (United Nations Development Program) Development of human and natural resources in poor countries. Headquarters in New York

Various Ministries Assisting in Health Programs

MOHFW (health and family welfare)
Vit. A, prophylaxis Nutritional anemia prophylaxis IDD control Food Safety and Standards Authority of India (FSSAI), 2006
Women and child development (under HRD)
ICDS program
Social welfare
Special nutrition program Balwadi nutrition program
Education ministry
Midday meal progra

Number per population

Category	Norms suggested
Doctors	1 per 3500 population
Nurses	1 per 5000 population
Health worker female and male	1 per 3500 population in plain and 3000 population in hilly areas
Trained dai	One for each village
Health assistant (male and female)	1 per 30,000 population in plain area and 1 per 20,000 population in tribal and hilly areas Provides supportive supervision to 6 health workers (male and female)
Pharmacists	1 per 10,000 population
Lab technicians	1 per 10,000 population
ASHA (accredited social health activist)	1 per 1000 population

FEW NUTRITION DEFINITIONS

- **Tolerable Upper Intake Level (UL)**: The highest average daily nutrient intake level that is likely to pose no adverse health effects for almost all individuals in the general population.

Recommended Dietary Allowance (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97.5% OR *mean + 2 SD*) healthy individuals in a particular life stage and gender group.

Adequate Intake: A recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people - used when RDA cannot be determined; in the Indian context, this is the "acceptable intake".

Estimated Average Requirement (EAR): The average daily nutrient intake level estimated to meet the requirement of half of the healthy individuals in a particular life stage and gender group.

RECOMMENDED DAILY ENERGY AND PROTEIN INTAKE

Group	Particulars	Energy (Kcal/day)	Proteins (g/day)
Adult male	Sedentary worker	2320	60
	Moderate worker	2730	60
	Heavy worker	3490	60
Adult female	Sedentary worker	1900	55
	Moderate worker	2230	55
	Heavy worker	2850	55
	Pregnancy	+350	+23
	Lactation (0-6 m)	+600	+19
Infants	Lactation (6-12 m)	+520	+13
	0-6 months	92/kg	1.16/kg
	6-12 months	80/kg	1.69/kg

REFERENCE INDIAN MAN AND WOMAN

	Reference Indian Man	Reference Indian Woman
Age	18-29 years	18-29 years
Weight	60 kg	55 kg
Height	1.73 m	1.61 m
BMI	20.3	21.2
Others	Free from disease, fit for active work, engaged in 8 hours of occupation (usually moderate activity), 8 hours in bed, 4-6 hours in sitting and moving about and 2 hours in walking and in active recreation or household activities	

MORE ONE-LINERS

- Sources of **energy**
 - Proteins : 4 kCal/g
 - Fat : 9 Kcal/g
 - Carbohydrate : 4 kCal/g
 - Dietary fibre : 2 kCal/g
- In a **balanced diet**:
 - Proteins = 10-15%
 - Fats = 15-30%
 - Carbohydrates = 50-70%
- A **consumption unit** is a coefficient of dietary intake, which varies between individuals on the basis of their age, sex and physical activity.
- **Soyabean** has **highest protein** content per 100 gm (43g/100gm).
- **Protein energy ratio (PER)** = energy from protein/total energy in diet X 100
- **DIAAS** (Digestible Indispensable Amino Acid Score) is the current accepted measure of protein quality.
- **NPU** (Net protein utilization) is the best indicator of protein quality.
- In calculating NPU, 1 gram of protein is assumed to be equivalent to 6.25 gram of protein.
- NPU of egg is 96. Egg protein is used as **standard or reference** for evaluating the protein from other diet sources.
- $NPU = BV \times DC / 100$. - Biological value X Digestibility Coefficient/100.
- Amino acids most deficient in proteins of a food item are 'limiting amino acids'.
- Richest source of essential fatty acids is **Safflower oil**.
- Richest source of Linoleic acid is **Safflower oil**.
- **Maximum content of PUFA** is found in **safflower oil**.
- Maximum content of **Saturated fatty acids** is found in **coconut oil**.
- **Halibut liver oil** is richest source of vitamin A and vitamin D.
- Limiting amino acid in soyabean is methionine.
- Food standards in India are based on **codex alimentarius**.
- **Ragi** is one of the **cheapest millets**; used **widely in AP and Karnataka**; it is **richest in calcium**.
- The base of the food guide pyramid is formed by **cereals and pulses**.

Food Items	Limiting Amino Acids
Cereals	Threonine (and lysine)
Pulses	Methionine (and cysteine)
Maize	Tryptophan (and lysine)

IODINE AND SALT

- Recommended **fluorine** level in drinking water in India = **0.5 - 0.8 mg/litre**.
- Fluorine** is a **double edged sword**.
- Iodine requirement = 150 microgram/day.
- Urinary iodine levels - principal impact indicator.
- In India, under the Prevention of Food Adulteration (PFA) act, the level of iodization is fixed to be **not less than 30 ppm at the production point** and **not less than 15 ppm at the consumer level**.
- Himalaya goiter belt** - World's largest goiter belt extending from Kashmir to Naga hills, about 2400 km.
- In one particular **district (Gonda) of Uttar Pradesh** known to be **highly endemic**, the **prevalence of neonatal hypothyroidism** has been measured at extremely high **rate of 15%**.
- "Two-in-one" salt** = common salt fortified with **iron and iodine**.

FOOD TOXICANTS

Disease	Food	Toxic agents
Neuro-lathyrism	Lathyrus sativus (kesari dal)	N-Beta-oxalyl amino alanine (prevented by Vitamin C prophylaxis)
Epidemic dropsy	Mustard oil contaminated with argemone oil	Toxic alkaloid sanguinarine in argemone oil
Endemic ascites	Millets contaminated with weed seeds <i>Crotalaria</i> (jhunjunia)	Pyrrolizidine alkaloids in weeds which are hepatotoxic
Fusarium toxins	Sorghum contaminated with fungus <i>Fusarium incarnatum</i> which produce the toxic metabolites	
Hepato-toxicity	Food grains	Aflatoxins produced by <i>Aspergillus</i> fungi
Ergotism		<i>Claviceps fusiformis</i>

TYPES OF VENTILATION

Plenum ventilation	Fresh air is blown into the room by centrifugal fans so as to create a positive pressure, and displace the vitiated air. Plenum or propulsion system is used for supplying air to air-conditioned buildings and factories. Air is delivered through ducts at desired points. This system is of limited utility.
--------------------	--

Exhaust ventilation

Air is extracted to the outside by exhaust fans driven by electricity. As air is extracted, a vacuum is created which induces fresh air to enter the room through windows doors and other inlets. Used in halls, auditoria.

Balanced ventilation

A combination of exhaust and plenum types

TRIAGE COLOR CODES

Triage is classification of patients based on **severity of injury**.

Red	Immediate (High priority treatment or transfer)
Yellow	Urgent care (Medium priority)
Green	Delayed Care (Ambulatory patients)
Black	Dead patients

DISASTER

- There are three fundamental aspects of disaster management:
 - Disaster response
 - Disaster preparedness
 - Disaster mitigation
- These three aspects of disaster management correspond to different phases in the so-called 'disaster cycle' shown below.
- Preparedness → Response → Rehabilitation → Reconstruction → Mitigation → Preparedness.**

OTTAWA CHARTER

Five action areas for health promotion were identified in the **Ottawa Charter for Health Promotion 1986**:

- Building healthy public policy
- Creating supportive environments
- Strengthening community action
- Developing personal skills
- Reorientating health care services toward prevention of illness and promotion of health

SPECTRUMS

- Spectrum of health:** Health and disease lie along a continuum and there is no single cut off point. The lowest point on the health disease spectrum is death and the highest point corresponds to the WHO definition of positive health.
- Spectrum of disease:** is a graphic representation of the various manifestations of a disease - similar to the spectrum of light where the colors vary from one end to the other, but difficult to determine where one colour ends and the other color begins.

HEALTH INDICATOR

(Characteristics of an **ideal health indicator** should be as below:

- Valid:** it must measure what it is supposed to measure.
- Reliable:** the answer should be the same if measured by different people in similar circumstances.
- Sensitive:** they should be sensitive to changes in the situation concerned.
- Specific:** they should reflect changes only in the situation concerned.
- Feasible:** they should have the ability to obtain data needed
- Relevant:** they should contribute to the understanding of the phenomenon of interest.

Steps of planning cycle

- Analysis of health situation
- Establishment of objectives and goals
- Assessment of resources
- Fixing priorities
- Write-up of formulated plan
- Programming and implementation
- Monitoring
- Evaluation

MANAGEMENT METHODS AND TECHNIQUES

Methods based on behavioral sciences	Quantitative methods
Organizational design	Cost benefit analysis
Personnel management	Cost effectiveness analysis
Communication	Cost accounting
Information systems	Input output analysis
Management by objectives	Model
	Systems analysis
	Network analysis
	Program evaluation and review technique (PERT)
	Critical path method (CPM)
	Planning Programming
	Budgeting system (PPBS)
	Work sampling
	Decision making

Few Management Methods Explained

- Cost benefit analysis:**
 - This has received the widest attention for **application in health field**.
 - The economic benefits of any program are compared with the costs of that program.

- Cost effectiveness analysis:**

- This is a more promising tool; it is similar to cost benefit analysis except that, benefit instead of being expressed in monetary terms is expressed in terms of results achieved (e.g., no. of lives saved).

- Cost accounting**

- Provides basic data on cost structure of any program.
- Financial records are kept in a manner permitting costs to be associated with the purpose for which they are incurred.

- Input-output analysis:**

- This is an economic technique. In the health field "input" refers to all health service activities which consume resources (manpower, money, materials and time); and "output" refers to such useful outcomes as cases treated or lives saved

- Work sampling:**

- This is a systematic observation and recording of activities of one or more individuals carried out at pre-determined or random intervals. It provides quantitative measurements of the various activities.

TARGETS AND GOALS

- An objective (point)** is precise; it is either achieved or not achieved; it is **the planned end point of all activities**.
- Target** often refers to a **discrete activity** such as the number of blood films collected, etc.
- Goals:** Is the **ultimate desired state** toward, which **objectives and resources are directed**.

THE FACTORIES ACT, 1948

- The act defined factory as an establishment employing **10 or more persons where power is used** or **20 or more persons where power is not used**.
- Employment of persons **below age of 14 years** is prohibited.
- Persons between 15-18 years of age may be declared fit by 'certifying surgeons' - will work **ONLY** between 6 AM to 7 PM.
- Hours of work:
 - A maximum of 4.5 hours of work/day for adolescents.
 - 48 hours/week (9 hours/day)
 - Maximum **60 hours per week** (including overtime)
- Safety recommendations:
 - 500 cubic feet of space/worker

- 1 **safety officer**/1000 workers
- 1 **welfare officer**/500 workers
- 1 **canteen** for > 250 workers
- 1 **creche** for > 30 women workers.
- Under factories act there are 29 *diseases* that are *notifiable (schedule 3)* including silicosis, byssinosis, asbestosis and anthracosis.

ESI ACT, 1948

- ESI Act covers all factories *except mines, defense and railways*.
- ESI act covers all employees getting income upto **Rs.21,000/month**.
- The **Union minister for labor** is the **Chairman** of the ESI corporation.
- Employer contributes 4.75% of total wage bill.
- Employee contributes 1.75% of total wage bill (those earning rs.100/day are exempted).
- State and central govt. share medical expenditure in a **ratio of 1:7**.
- Benefits to employees under ESI:
 - Medical benefit - full medical care
 - **Sickness benefit**: 70% of the average daily wages is payable for 91 days (in any continuous period of 365 days).
 - **Extended sickness benefit**: payable for 2 years for a set of 34 diseases.
 - **Enhanced sickness benefit**: full average daily wage for duration of upto 7 days in the case of vasectomy and upto 14 days in the case of tubectomy.

Categories of Biomedical Waste (BMW) and Color Coding

Color	Waste material
Yellow (non-chlorinated plastic cover of 50 microns)	<ul style="list-style-type: none"> • Human and animal anatomical waste • Soiled waste (cotton swabs, dressings, bedding, linen, etc.) • Blood bags • Microbiological, clinical and lab waste (includes culture media, vaccines, cell cultures, toxins) • Discarded medicines • Cytotoxic drugs • Items contaminated with cytotoxic drugs
Red (non-chlorinated plastic cover of 50 microns)	<ul style="list-style-type: none"> • Gloves • Tubings • Bottles • Urine bags • Syringes (without needles) • Vacutainers
Blue cardboard box with blue marking (NO blue covers)	<ul style="list-style-type: none"> • Broken glass-medicine vials and ampoules • Metallic body implants

BIO-MEDICAL WASTE DISPOSAL

Biomedical Waste Management (BMW) in India

- Biomedical Wastes (BMW) in India are handled and managed under 'Biomedical Waste Management (Management and Handling) Rules, 1998. BMW rules were amended in 2016
- Exercising powers: Section 6, 8, 25 of 'Environment (Protection) Act, 1986' (under the Ministry of Environment and Forests)
- **10%-25% health care waste is regarded as hazardous.**



Fig. 14.6: Symbols

Color	Waste material
White translucent puncture-proof container	<ul style="list-style-type: none"> • Needles • Scalpel blades • Burnt needles • Syringes with fixed needles
Liquid biomedical waste from OT, labs	<ul style="list-style-type: none"> • Pretreat with 10% sodium hypochlorite and send to sewage treatment plant before letting out in general drainage



Fig. 14.7: Pesticide toxicity labels

Incineration of Waste

Wastes suitable for incineration	Wastes NOT to be incinerated are
<ul style="list-style-type: none"> • Low heating volume—above 2,000 kcal/kg for single chamber incinerators and above 3,500 kcal/kg for double chamber incinerators • Content of combustible matter above 60% • Content of non-combustible solids below 5% • Content of non-combustible fines below 20% • Moisture content below 30% 	<ul style="list-style-type: none"> • Pressurized gas containers • Large amount of reactive chemical wastes • Silver salts and photographic or radiographic wastes • Halogenated plastic such as PVC • Wastes with high mercury/cadmium content such as broken thermometers, used batteries and lead-lined wooden panels • Sealed ampoules or ampoules containing heavy metals.

EXTRA EDGE

- Expired **cytotoxic drugs and items contaminated with cytotoxic drugs** to be **returned back to the manufacturer or supplier for incineration at temperature >1200 degrees C** or to common bio-medical waste treatment facility or hazardous waste treatment, storage and disposal facility for **incineration** at >1200 degrees C Or **Encapsulation or Plasma Pyrolysis** at >1200 degrees C.

EPIDEMIOLOGY

- **Descriptive epidemiology** deals with the formulation of etiological hypothesis.
- **Analytical epidemiology** deals with testing the etiological hypothesis and identifying the underlying causes or risk factors of disease.
- **Analytical studies** are of two types of **observational studies**: Cohort study and case control study.



Fig. 14.8: John Snow — Father of Modern Epidemiology

ALL ABOUT STUDIES

Sampling Methods

Simple random sample	This is done by assigning a number to each of the units (individuals or households) in the sampling frame. A table of random numbers is then used. This technique provides the greatest number of possible samples
Systematic random sample	This is done by picking every 5th or 10th unit at regular intervals . e.g. To carry out a filaria survey in a town we take a 10 per cent sample. By this method each unit in the sample would have the same chance of being selected, but the number of possible samples is greatly reduced.
Stratified random sample	The sample is drawn in a systematic way so that each portion of the sample represents a corresponding strata of the universe, e.g. this method is used when one is interested in analysing the data by a certain characteristic of the population, viz. Hindus, Christians, Muslims, age-groups etc... – as we know these groups are not equally distributed in the population.
Cluster Random Sample	Used in India for <i>evaluation of Immunization coverage</i> ; 30 X 7 technique used

- The sampling error is not the only error, which arises in a sample survey.
- **Non-sampling errors** given below are more important than sampling errors:
 - *Inadequately calibrated instruments*
 - *Observer variation*
 - *Incomplete coverage achieved in examining the subjects selected*
 - *Conceptual errors.*

Study Designs

- **Cross-sectional study**: based on single examination of a cross-section of population at **one point in time** – also called as prevalence study. This tells us about distribution of disease rather than etiology.
- **Longitudinal study**, observations are repeated over a prolonged period of time by means of follow-up examinations. Useful for finding out the incidence of new cases.
- **Single blind trial** the participant is not aware whether he belongs to the study group or control group.
- **Double blind trial** neither the doctor nor the participant is aware of the group allocation or the treatment received. This is the most frequently used method.

- **Triple blinding** (ideally should not be used), the participant, investigator and the person analyzing the data are completely blind.

Case – Control and Cohort Studies

Case-control study	Cohort study
Observational and retrospective	Observational and prospective)
Proceed from "effect to cause" (Comparison of patients with disease to healthy controls; frequency of certain exposures in both groups is considered)	Proceeds from "cause to effect" (Examines a group exposed to a given risk factor to a group without to assess whether risk factor the likelihood of disease Exposed group identified and followed over time)
Suitable for rare diseases	Suitable for common diseases (e.g.: Coronary Heart disease in Framingham Study)
Short study time	Prolonged study time
Smaller number of subjects	Large number of subjects
Yields only odds ratio	Yields <i>incidence rates, relative risk as well as attributable risk</i>
More chance for bias	Less selection bias occurs
Relatively inexpensive	Expensive
No volunteer subjects needed	Regular follow up of participants needed
Susceptible to recall and selection bias	Can study multiple effects of exposure

Evidence-Pyramid in Research (From Top to Bottom)

- Meta-analysis (Highest clinical relevance GOLD STANDARD)
- Systematic review
- Cohort study
- Case control study
- Case series
- Case report
- Ideas, Editorials, Opinions
- Animal research
- In-vitro (test-tube) research (Lowest clinical relevance)

Study Designs Used in Clinical Research

Study type	Description	Measures/ examples	Advantages	Disadvantages
Cross-sectional study (Observational)	Survey of a large number of people at one point in time to assess exposure and disease prevalence	Disease prevalence and a hypothesis for risk factors Asks – "What is happening?"	Can be used as an estimate for disease prevalence following exposure	Cannot be used to test hypothesis, does not establish causality
Randomized control trial (RCT)	Prospective comparison of experimental treatment to placebo controls and existing therapies Double blinded to avoid bias Randomization takes care of the effects of unknown confounders Patients randomized into study groups	Effectiveness of experimental treatment compared to controls and existing therapies	Gold standard for testing therapies May be controlled for several confounders	Often costly and time consuming, and patients may not be willing to undergo randomization
Meta-analysis	Pooling of data from multiple studies examining a given disease or exposure to come to an overall conclusion	Depends on original study type	Larger study size Achieves greater statistical power and integrates results of similar studies Can resolve conflicts in literature	Unable to eliminate limiting factors in original studies

Types of Bias in Clinical Studies

Type of bias	Description	Consequences
Selection (enrolment)	Nonrandom assignment of subjects to study groups	Results of the study may not be applicable to the general population
Investigator	Subjective interpretation of the data by investigator deviates toward 'desired' conclusions	Results of study will incorrectly resemble the proposed hypothesis
Lead-time	A screening test provides an earlier diagnosis in the study group when compared to controls but has no effect on time of survival	Time from diagnosis to outcome increases because earlier diagnosis causes the false appearance of an increased time of survival; time from beginning of disease to the outcome actually remains the same regardless of screening
Observational	Subjects may respond to subjective questions in a different way than normal since their awareness of the study changes their perception of the examined issue	Effectiveness of therapy is not accurately depicted by study group
Length	A screening test detects several slowly progressive cases of a disease but misses rapidly progressive cases	Effectiveness of screening test is overstated
Recall or Memory Bias	Errors of memory within the subject occurs due to prior confounding experiences	Patients with negative experiences are more likely to recall negative details
Publication	Studies that show a difference between two groups are more likely to be published than studies that do not show a difference	Data available for meta-analysis may not include studies that support the null hypothesis

Type of bias	Description	Consequences
Self selection	Patients with a certain past medical history may be more likely to participate in a study related to their condition	Subjects are not representative of the general population and introduce confounding variables
Berksonian Bias	Named after Dr Joseph Berkson who recognized this problem. This bias arises because of the different rates of admission to hospitals for people with different diseases (i.e. hospital cases and controls)	
Interviewer's bias	Occurs when the interviewer knows the hypothesis and knows who the cases are	Can be eliminated by double blinding
Neymann bias	Bias due to missing of fatal cases, mild/ silent cases and cases of short duration of episodes from the study	
Attention bias (Hawthorne effect)	Study subjects may systematically alter their behavior when they know they are being observed	
Apprehension bias	Certain levels (pulse, blood pressure) may alter systematically from their usual levels when the subject is apprehensive	

Tools of Measurement in Epidemiology

- **Rate:** Numerator (a) is a part of denominator (b) and multiplier is 1000 or 10,000 or 100,000 or so on.
- **Ratio:** Numerator (a) is not a part of denominator (b) and BOTH numerator and denominator are unrelated
- **Proportion:** Numerator (a) is a part of denominator (b) and multiplier is 100.

Parameter	Formula	Numerator (N) & Denominator (D)	Conclusion
Infant mortality rate (IMR)	No of infant deathsX1000 No of Live births	N is a part of D; multiplier NOT 100	Rate
Maternal mortality rate (MMR)	No of maternal deaths X 100000 No. of Live births	N is NOT part of D; both unrelated	Ratio
Sex ratio	No of females x 1000 No of males	N is NOT a part of D; both unrelated	Ratio
Incidence	No of new case x 1000 Total population risk	N is a part of D; multiplier NOT 100	Rate
Prevalence	No of new+ old cases X 100 Total population	N is a part; multiplier 100	Proportion
Case fatality rate (CFR)	No of deaths X 100 No of cases	N is a part of D; multiplier 100	Proportion
Relative risk (RR)	incidence among exposed Incidence among non-exposed	N is NOT a part of D; both unrelated	Ratio

Case Fatality Rate (CFR)

- CFR represents '**killling power of a disease.**' It is closely related to '**virulence**' of organism.
- $CFR = \frac{\text{Total no. of deaths due to a disease}}{\text{Total no of cases due to a disease}} \times 100$
- CFR is a **Proportion**: Always expressed in **Percentage**.
- CFR is the '**complement of Survival Rate**', thus $CFR = 1 - \text{Survival Rate}$
- CFR of few important diseases: **Rabies (100%); Yellow fever (80%); Japanese encephalitis (30-35%); Chicken pox (<1%)**.
- **Limitations of CFR:**
 - Time interval is NOT specified
 - CFR typically used in **acute** infections (limited usefulness for chronic diseases)
 - CFR for the same disease may vary in different epidemics due to changes in agent, host and environmental factors.

Confounding

- **Confounding Factor:** Any factor associated with both exposure and outcome, and has an independent effect in causation of outcome is a confounder:
 - It is found unequally distributed between the study and control groups
 - Is associated with both exposure and outcome
 - Has an independent effect in causation of outcome (thus a risk factor itself).

Methods Used to Control Confounding

Method	Utility of control confounding
Randomization	Most ideal method
Restriction	Limiting study to people who have particular characteristics
Matching	Mostly useful in case control studies
Stratification	Useful for larger studies
Statistical modelling	When many confounding variables exist simultaneously

Hill's (Surgeon General's) Criteria of Causal Association

- **Temporal association:** Implies 'cause precedes effect' or 'effect follows cause':
 - Consider both 'order of appearance' as well as 'length of interval between exposure and disease.'

- Is 'most important criterion' of causal association
- Is 'best established by a cohort study' (Especially Concurrent cohort study)
- **Strength of association:**
 - Relative risk (cohort study)
 - Odds ratio (case control study)
- **Specificity of association:** Implies that disease under study is caused only by risk factor under study
 - Is 'most difficult criterion to establish'
 - Is 'weakest criterion of causal association'
- **Consistency of association:** Implies that results are replicable in different settings and by different methods
- **Biological plausibility:** implies existence of biological credibility of association (anatomically, physiologically explainable / justifiable)
- **Coherence of association:** Implies that increase in dose of cause increases incidence/ prevalence of effect
- **Cessation of exposure:** Reversibility: Implies that removal of possible cause reduces the risk of disease
- **Study design:** Implies that if study design is based on a strong study design.

MORE ONE-LINERS

- **Soiling index** is used for **monitoring air pollution**.
- **District Mental Health Program (DMHP)** is an approach to decentralize mental health care in the community using the public health infrastructure and other resources.
- This model has been **pilot tested in Bellary District of Karnataka State** and found to be very useful to address the basic mental health needs of the population.
- A **daily supply of 150-200 liters per capita** is considered as an adequate supply to meet the needs for all urban domestic purposes.
- Tests of pasteurized milk are:
 - Phosphatase test
 - Standard plate count
 - Coliform count
- The permissible dose of radiation from man sources **should NOT exceed 5 rads/year**.
- The **denominator for all specific death rates** is the **mid-year population** and the **multiplier is 1000**.
- **Estimated number of annual pregnancies** in a subcentre catering to population of 5000 with crude birth rate of 25 per 1000 population is 130 [(25 X 5000)/1000 = 125 births + 13 pregnancy wastage = 130]
- **STEP wise approach to surveillance (STEPS):** Is a simple, standardized method by WHO for surveillance of **risks factors for chronic non-communicable diseases** (ex: coronary heart disease etc...).

Institutes of Public Health Importance in India

Institute	Location
Central Drug Research Institute (CDRI)	Lucknow
Central Leprosy Training & Research Institute (CLTRI)	Chengalpattu
Central Research Institute	Kasauli
Haffkine Institute	Mumbai
LRS Institute of T.B & allied Diseases	New Delhi
National Tuberculosis Institute (NTI)	Bangalore
National Environment Engineering Research Institute (NEERI)	Nagpur
National AIDS Control Organisation (NACO)	New Delhi
National Institute of Communicable Disease (NICD)	New Delhi
National Institute of Virology (NIV)	Pune
National Institute of Nutrition (NIN)	Hyderabad
National JALMA Institute for Leprosy	Agra
National Institute of Occupational Health (NIOH)	Ahmedabad
National Institute of Mental Health and Neurosciences (NIMHANS)	Bangalore
Tuberculosis Research Institute (TRC)	Chennai

Instruments of Importance in Public Health

Instrument	Use
Ice Lined Refrigerator (ILR)	Cold chain temperature maintenance
Dial Thermometer	Cold chain temperature monitoring
Horrock's Apparatus	Chlorine demand estimation in water
Chlorination, Chloronome	Mixing/regulating the dose of chlorine in water
Chloroscope	Measuring level of residual chlorine in drinking water
Winchester Quart bottle	Assess physical and chemical quality of drinking water
Kata Thermometer	Assess cooling power of air and air velocity (Latter Currently)
Anemometer	Assess air/wind velocity
Hygrometer and Sling Psychrometer	Assess air humidity (moisture content in air)
Assman Psychrometer	Assess air humidity
Mercurial Barometer	Atmospheric pressure
Aneroid Barometer	Atmospheric pressure
Wind Vane	Assess air/wind direction
Sound Level Meter	Measures Intensity of sound
Band Frequency Analyzer	Characteristic of sound (pitch)
Audiometer	Hearing ability assessment
Salter's scale	Field Instrument for Low Birth Weight (LBW)

Contd...

Contd...

Instrument	Use
Infantometer	Length of infants
Stadiometer	Height of adults
Shakir's Tape	Mid-Arm Circumference (MAC)
Symon's rain gauge	Measures precipitation (rain, snow, hail, dew, frost)

Important Days of Public Health Importance

30 th January	Anti-Leprosy Day
10 th February	National Deworming day
2 nd Wednesday of March	No Smoking Day
8 th March	International Women's Day
15 th March	World Disabled Day
24 th March	Anti-TB Day
7 th April	World Health Day
25 th April	World Malaria Day
8 th May	World Red Cross Day
31 st May	No Tobacco Day
5 th June	World Environment Day
14 th June	World Blood Donor Day
26 th June	International Day Against Drug Abuses and Illicit Trafficking
1 st July	Doctors Day
11 th July	World Population Day
28 th July	World Hepatitis Day
8 th September	World Literacy Day
28 th September	World Rabies Day
1 st October	National Voluntary Blood Donation Day
1 st October	International Day for Older Persons
2 nd Wednesday of October	World Disaster Reduction Day
9 th October	World Sight Day
10 th October	World Mental Health Day
24 th October	UN Day
10 th November	Universal Immunization Day
25 th November	International Day for Elimination of Violence against Women
1 st December	World AIDS Day
3 rd December	International Day of Disabled Persons
10 th December	Human Rights Day
2 nd week of March	World Glaucoma Awareness week
Last Week of April	World Immunization Day
1-7 th May	Anti-Malaria Week
1-30 th June	Anti-Malaria Month
1-8 th August	World Breast Feeding Week
25 th August -8 th September	Eye Donation Fortnight
15-21 st November	Newborn Care Week



Fig. 14.9: NACO logo



Fig. 14.13: National health mission



Fig. 14.10: Aids awareness symbol - red ribbon



Fig. 14.14: DOTS

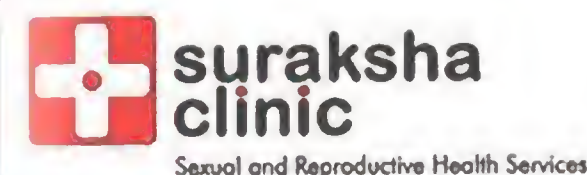


Fig. 14.11: Suraksha clinic

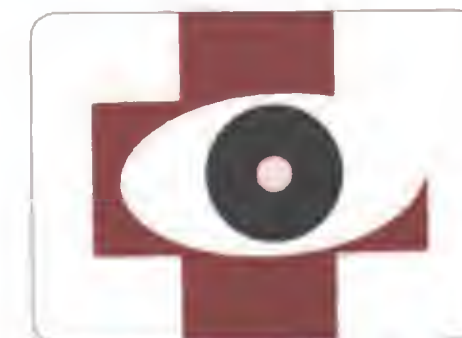


Fig. 14.15: NPCB logo



Fig. 14.12: PPTCT logo



Fig. 14.16: UNESCO



Fig. 14.17: WHO



Fig. 14.21: NDMA logo - Chairman is the PM of India



Fig. 14.18: UNICEF



Fig. 14.22: NLEP logo



Fig. 14.19: FAO



Fig. 14.23: IDCF logo



Fig. 14.20: RSKS logo

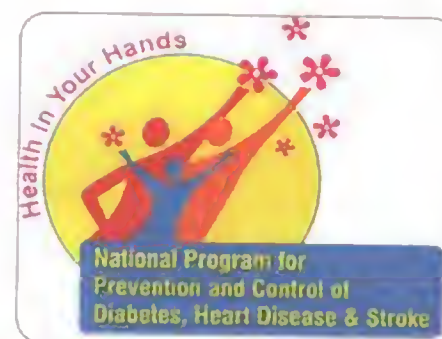


Fig. 14.24: NPCDCS logo



Fig. 14.25: NVBDCP logo



Fig. 14.28: NIDDCP LOGO



Fig. 14.26: RKSK logo



Fig. 14.29: PMSMA logo



Fig. 14.27: Mission Indradhanush logo

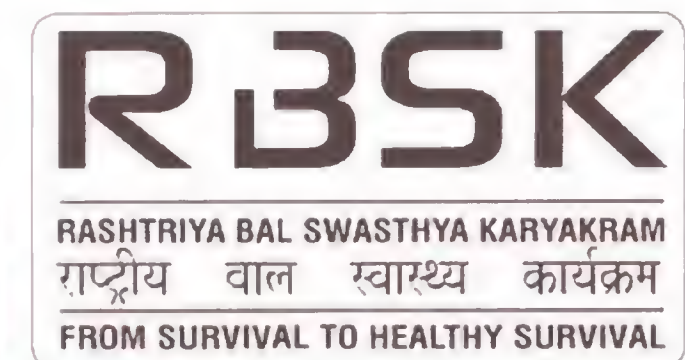


Fig. 14.30: RBSK logo

Forensic Medicine

IMPORTANT DATES

Act/Event	Date
Indian Penal Code (IPC)	1860
Indian Evidence Act (IEA)	1872
Criminal Procedure Code (CrPC)	1973
Indian Lunacy Act	1912
Indian Mental Health Act	1987
The Poisons Act	1919
Drugs and Cosmetics Act	1940
First fingerprinting bureau in the world	1897 (In Kolkata)
MTP Act	1971
Consumer Protection Act	1986
Indian Motor Vehicles Act	1988
Pre-natal Diagnostic Technique (PNDT) (Prevention of Misuse) Act	1994
Transplantation of Human Organs Act	1994
Juvenile Justice Act	2000 (original act) and 2015 (latest amendment after 'Nirbhaya' case)
Criminal Law (amendment) Act	2013 ('Re-definition' of rape and sexual offences)
Mental Healthcare Bill	2016 (This has 'decriminalized' the attempt to suicide by its section 124; Note: this was earlier a punishable offense under section 309 IPC)
MCI Act	1956 (original act) and 2016 (latest amendment approving NEET)

IMPORTANT SECTIONS OF IPC

Criminal responsibility (whether a person is responsible for crime or not)

46	Defines 'death'
82	Any act done by a child <7 years of age is not an offence
84	Criminal responsibility of insane – act of person with unsound mind is not an offence; McNaughten rule comes under this section
85	Act of an intoxicated person (e.g. drunk) is NOT an offence if he has been intoxicated against his will
86	Act of an intoxicated person (e.g. drunk) is criminally responsible if he had the intention/knowledge of the crime
87	A person above 18 years can give consent to suffer any harm which may result from an act not intended or not known to cause death or grievous hurt.
92	Implied consent (Act done in good faith for benefit of a person without consent—if the circumstances are such that it is impossible for that person to sign the consent, or if that person is incapable of giving consent, and has no guardian/relative from whom it is possible to obtain consent within time)—Ex: Dr X, a surgeon, sees a child suffer an accident which is likely to prove fatal unless an operation is immediately performed. There is no time to take consent from the child's guardian. A performs the operation intending, in good faith, the child's benefit. Dr X has committed NO offence
94	Act to which a person is compelled by threat is not an offence

Perjury, hostile witness and false certificate

191	Perjury (giving false evidence under oath) and hostile witness
193	Punishment for false evidence
197	Issuing or signing (attesting) false certificate by a doctor

Rape and sexual offences

375	Defines Rape
376	Punishment for rape (7 years to life imprisonment + fine)

Contd...

Contd...

376A	Punishment for causing death or persistent vegetative state of the victim due to rape (can be charged with death sentence)
376B	Punishment for Intercourse by a man with his wife during separation
376C	Punishment for sexual intercourse by a person in authority
376D	Punishment for Gang Rape (minimum 20 years)
376E	Punishment for repeat rape offenders
376A	Punishment for disclosure of identity of rape victim
374	Assault or criminal force to a woman with intention to outrage her modesty—Includes sexual harassment (354A) and punishment for it (354B) and voyeurism (354C)
366A	Procurement of minor girl for sexual intercourse
309	Word gesture or act intended to insult the modesty of a woman
394	Exhibitionism

Offences related to Hurt

309	Culpable homicide not amounting to murder (ex: <i>husband finds his wife in bed with another man and temporarily loses control of his mind and shoots him — 'hot blooded' murder</i>)
300	Murder, (Culpable homicide amounting to murder) (ex: <i>a person wanting to take revenge against his enemy deliberately follows him to a lonely place and kills him 'cold blooded murder'</i>)
302	Punishment for murder
304	Punishment of culpable homicide
307	Attempt to murder
309	Attempt to suicide (No longer valid)
314	Defines hurt
320	Defines Grievous Injury
324	Voluntarily causing hurt by dangerous weapon
325	Punishment for voluntarily causing grievous hurt
326A,B	Causing grievous injury/disfigurement by throwing of acid
338	Causing grievous hurt by act endangering life or personal safety of others
351	Assault

Dowry related offences

304-B	Dowry death (punishment from 10 years to life imprisonment) Note: As per dowry prohibition act (1961) taking dowry is punishable with imprisonment of at least 5 years and fine of at least ₹ 15,000
498-A	Punishment for cruelty by husband or relatives

Contd...

Contd...

Offences related to abortion and childbirth 312–315 IPC

312	Causing criminal abortion with patient's consent
313	Causing miscarriage without woman's consent
317	Abandoning a child
318	Concealment of birth by secret disposal of dead body

Others

53	An accused can be examined by medical practitioner at request of police even without his consent or by force
44	Injury
46	Definition of death
88-93	Legal protection to medical doctors
166A	Public servant disobeying direction under law
201	Embalming before autopsy is punishable
269	Negligent act likely to spread infection of disease dangerous to life.—Whoever unlawfully or negligently does any act which is, and which he knows or has reason to believe to be, likely to spread the infection of any disease dangerous to life, shall be punished with imprisonment of either description for a term which may extend to six months, or with fine, or with both. Ex: Physician injects HIV +ve needle into a normal healthy person.
304-A	Criminal negligence leading to death, medical negligence (maximum imprisonment is 2 years)
363	Punishment for kidnapping
377	Unnatural sexual offences (including sodomy)
379	Punishment for theft

CRIMINAL PROCEDURE CODE (CrPC)

CrPC prescribes the procedure for investigation and trial of criminal offences.

- 2(C) CrPC: deals with **cognizable offences**.
- 6–25 CrPC: constitution of criminal courts and officers.
- 26 CrPC: **division of offences**.
- 39 CrPC: If a doctor is convinced that the patient upon whom he is attending is suffering from homicidal poisoning, he is bound to inform the police.
- 53(2) CrPC: **Male doctor can examine Female** only in presence of female attendant
- 61–69 CrPC: **serving of summons or subpoena**
- 174 CrPC: **Police Inquest**.
- 176 CrPC: **Magistrate Inquest for dowry death**.
- 293 CrPC: **Exceptions to oral evidence**.
- 416 CrPC: **Postponement of execution/death/capital punishment of a pregnant woman**.

INQUEST

Police Inquest (Section 174 CrPC)

- *Inquest* is the legal or judicial enquiry to ascertain cause of death.
- *Police Inquest* is the MC type of inquest in India (inferior to magistrate inquest); done by the officer in charge of a police station; **NOT below the rank of a head constable** (usually a sub-inspector) — investigating officer (IO). After **informing the executive magistrate**, in the presence of 2 respectable inhabitants (*panchas*) and witnesses, he prepares the report of apparent cause of death (*panchnama* — has to be signed by IO). If no foul play is suspected, the body is handed over to the relatives; or else the body is sent for postmortem to find out the cause of death. IO (police) **may summon** the person for answering questions; **refusal to answer questions by police** is punishable under section 179 IPC.
- *Police Inquest* is done in
 - Death by **suicide**
 - Death by killing another person (**murder**) or an **animal**
 - Death by **accident**
 - Death under circumstances raising a **reasonable suspicion** that some other person has committed an offence.

Magistrate's Inquest (Sec 176 CrPC)

Done by an **executive magistrate, district magistrate**, or any **sub-divisional magistrate** (SDM)—it is superior to police inquest

- It is done in cases of
 - Death in **police custody/prison/ar** during **police interrogation**
 - Death due to **police firing**
 - **Dowry death** and
 - **Exhumation** cases (digging body out of grave)
 - **Dowry death** (death of woman within 7 years of marriage)
 - **Rope** in **police custody**.

Coroner's Inquest

- This was held only in **Mumbai till 1999**, not done now.
- Coroner's court is only a court of **inquiry**.
- Accused **NEED NOT be present** during the trial
- Coroner has **NO POWER** to impose fine or punish the accused.

Medical Examiner's System

- Practiced in USA, Canada, Japan BUT NOT in India

- Inquest is conducted by a medical person, BUT he does not have any judicial power
- It is the **best type** of Inquest overall.

COURTS

Types of Courts

1. Supreme Court

- Apex court of the country, established under **article 124** of Constitution of India.
- Located in New Delhi
- Presided by Chief Justice of India who is appointed by **President of India**.
- Can pass any sentence including capital punishment (death sentence).
- Considers appeals from all lower courts.

2. High Court

- Apex court of the state established under **article 214** of Constitution of India.
- Presided by Chief Justice of the state who is appointed by **President of India**.
- Can pass any sentence including capital punishment (death sentence).

3. Sessions Court

- Presided by district judge appointed by the high court
- Can try any offence and pass any sentence; BUT a **death sentence has to be confirmed by the high court**.

4. Assistant Sessions Court

- Usually located at **subdivision** in a district.
- Presiding officer is called as **Assistant Sessions Judge**.
- **Assistant sessions court** can pass all sentences including **unlimited fine** and **imprisonment UPTO 10 years** (but NOT **death sentence**).

5. Magistrate's Court

- They are of three types and their powers as per **Sec. 29 CrPC** is shown in the following table.
- REMEMBER: **Judicial Magistrate** is appointed by **High Court**; **Executive Magistrate** is appointed by **State Government (CrPC 20)**.

Class of Magistrate	Imprisonment	Fine
Chief Judicial Magistrate (Chief Metropolitan magistrate in metro cities)	Upto 7 years	Unlimited
I Class Judicial Magistrate (Metropolitan Magistrate in metro cities)	Upto 3 years	₹ 10,000
II Class Judicial Magistrate	Upto 1 years	₹ 5,000

Consumer Court

- In 1993, medical services were brought under the **Consumer Protection Act (1986)**.
- A complaint has to be **filed within 2 years** from the date on which a cause of action has arisen.
- The Act has prescribed time limit for deciding complaint by forum or commission—as far as possible within **3 months**.
- Any appeal should be filed **within 30 days** of the order (to the Supreme Court).
- The composition of consumer redressal agencies is shown in the following table.

Level of court	Jurisdiction for services
District forum	UPTO ₹ 20 lakhs
State commission	20 lakhs–1 crore
National commission	> ₹ 1 crore

Juvenile Court

- Juvenile court is for trial of **children below 18 years** of age.
- The **Juvenile Justice** (Care of Protection of Children) Act, 2015 has now come into force (and replaces the earlier act from the year 2000).
- **Juvenile Justice Board**: consists of
 - **1 Class Judicial Magistrate** (or metropolitan magistrate) with at least **3 years experience** and
 - Two social workers—out of whom at least one shall be a **woman**.
- '**Child in conflict with law**' means a child who is alleged or found to have committed an offence and who has not completed eighteen years of age on the date of commission of such offence.
- '**Heinous offences**' includes the offences for which the minimum punishment under the Indian Penal Code or any other law for the time being in force is **imprisonment for seven years or more**.
- The Juvenile Justice Board is given the option to transfer cases of heinous offences by such children to a **Children's Court (Court of Session)** after conducting preliminary assessment.
- The provisions provide for placing children in a '**place of safety**' both during and after the trial till they attain the age of 21 years after which an evaluation of the child shall be conducted by the Children's Court.
- After the evaluation, the child is **either** released on probation and if the child is not reformed then the child will be sent to a jail for remaining term.

PUNISHMENTS

The various types of **punishments** authorized by law as per section 53 IPC are:

- **Death Sentence**:
 - The method for **death sentence (capital punishment)** in India is **hanging till death**.
 - The power of **pardon for death sentence (amnesty)** lies with the **President** of India.
 - Death sentence, if passed by any lower court **MUST** be confirmed by the **High Court**.
 - Postponement of death sentence of a pregnant woman comes under **Sec 416 CrPC**.
- Imprisonment for life (regarded as equal to **20 years** in prison).
- Imprisonment—either rigorous (i.e. with hard labor and solitary confinement) or simple.
- Forfeiture of property.
- Fine: Maybe awarded alone or in combination with imprisonment.

EXTRA EDGE

- **Double Jeopardy**: No person can be prosecuted and punished for the same offence more than once. **Article 20(2)**, Constitution of India.

OFFENSES

Non-cognizable offense, (Sec 20 CrPC): For arresting a person, warrant from the magistrate is necessary without which a police officer **CANNOT** arrest a person.

Cognizable offense

Cognizable offense, [Sec 2(C) CrPC]: An offense in which a police officer **CAN** arrest person **without warrant** from magistrate. Cognizable offences include:

- Rape and sexual harassment
- Murder and attempt to murder
- Ragging
- Grievous injury
- Public servant disobeying direction under law
- Dowry death.

Other Important Points in Medicolegal Procedure

- The part bringing the action in a civil case, i.e. **party filing the case in a civil court** is called the '**plaintiff**'. The accused is called '**defendant**' both in civil and criminal cases.

- **Subpoena** or **Summons** is a **legal document** compelling the attendance of a witness in a court of law under penalty on a particular day, time and place for the purpose of giving evidence. **Sec 61-69 CrPC** deals with summons.
- **Conduct money** is the fee paid to a witness in **civil cases** at the time of serving summons to meet expenses towards attending court; it is **paid by the party calling him**. Judge decides the conduct money in civil cases. In **Criminal cases** **No fee** is paid to the witness.

EVIDENCE

Dying declaration – S.32, IEA

- Made to the medical officer/ magistrate/village headman/ police/any other person
- Oath is NOT necessary
- Presence of accused is NOT needed
- Cross-examination is not possible
- Has a lesser legal value

Dying deposition

- Made only to **magistrate**
- **Oath** is necessary
- **IN presence** of Accused/his lawyer
- **Cross-examination** permitted
- Has a **more legal value**

EXTRA EDGE

- If a patient survives after having given 'dying declaration,' then it is not admitted as 'dying declaration' in the court of law—but has only **corroborative value**.
- **Death certificate** contains the **cause** of death, **manner** of death and **time** of death BUT NOT the mode of death.

Oral Evidence

- **Oral evidence** is more important than documentary evidence as it **permits cross-examination**.

Exceptions to oral evidence

- Dying declaration
- Expert opinion expressed in treatise
- Evidence recorded in lower court or in a previous judicial proceeding
- Public records (e.g. birth and death certificate, marriage certificate)
- Hospital records
- Evidence of mint officer
- Reports of certain govt. scientific experts: Chemical examiner; Chief Inspector of Explosives; Director of fingerprint bureau; Director of Central Forensic Science Lab or SFSL; Director of Haffkine institute, Mumbai; Serologist to the government.

- **Res gestae** is an exception to hearsay evidence; remarks made by the victim at the time of or immediately after crime are admissible as evidence, e.g. statement made to people at scene of crime or to physician in hospital.
- **Perjury** is the willful giving of false evidence by witness while under oath—**section 191 IPC**.
- A **medical man (doctor)** is considered as **both an expert and a common witness**.
- **Medical certificate** is **documentary evidence**.
- **Dichotomy** means **fee splitting**.
- Professional secrecy refers to the doctor's obligation to keep secret all the information regarding patient that he comes to know in the course of his professional work.
- **Privileged communication**: Some situation where the doctor has to reveal the patient's information to some authorities is known as privilege communication; it is an exception to professional secrecy.
- **Exceptions to professional secrecy (conditions where privileged communication holds good)** are:
 - **Notifiable infectious diseases**
 - **Venereal diseases**
 - **Servants and employers** (e.g. train signal man with color blindness)
 - **Suspected crime**
 - **Self-interest** (patient threatening doctor)
 - **Patient's own interest** (suicidal tendencies)
 - **In court of law**.
- **Euthanasia** means mercy killing.

Recording of Evidence

- Evidence is presented in **systematic order**
- 1. **Oath**: Compulsory to swear by god.
- 2. **Examination in chief**: Examination of witness by party who called him; in criminal cases the public prosecutor commences this examination.
- 3. **Cross-examination**: Examination of the prosecution witness by the opposite party (**defence lawyer/defence counsel**). **Leading questions** are permissible during **cross-examination** (Leading questions **NOT** allowed during Exam in chief and re-exam).
- 4. **Re-examination**: Examining the witness again after the cross-examination by the RH party who called him.
- **Questions by the Judge/Court/Presiding Officer**: Judge may ask questions to witness **at any stage of the trial**.

NEGLIGENCE

Medical Negligence

Medical negligence requires the plaintiff (i.e. the patient or relative if the patient has died) should establish the following **4Ds**:

- **Existence of the doctor's Duty** to the plaintiff based on existence of the doctor-patient relationship.
- **Applicable standard of care and its violation** (Dereliction of Duty).
- **Direct causation** (failure to exercise a duty of care must lead to damage)
- **Damage** (a compensable injury).

- **Medical negligence**: Absence of reasonable care and skill or willful negligence of a medical practitioner in the treatment of a patient which causes bodily injury or death of the patient.
- In **civil negligence** the **onus of proof lies on the plaintiff (patient)**; a civil wrong is known as '**tort**'.
- **Res Ipsa Loquitur**: Ordinarily, the professional negligence of a physician has to be proved in a court by the expert evidence of another physician. The patient **NEED NOT** prove negligence in cases where the rule of '**res ipsa loquitur**' applies, which means, '**the thing or fact speaks for itself**' (like scissors being left inside abdomen!); used in cases of **criminal negligence**; here the **onus of proof is on the doctor**. **Doctrine of common knowledge is a variant** of res ipsa loquitur.
- For criminal negligence, suit against doctor must be **filed within 2 years**.
- **Therapeutic misadventure** is a case in which an individual has been injured or had died due to some **unintentional act by a doctor** — due to **inherent risk of the procedure or the drug**.
- **Vicarious liability** is liability for the act of another.
- **Contributory negligence** is **not** a defence in criminal negligence.
- **Professional death sentence** (permanent removal from State Medical Council register) or penal erasure (for professional misconduct): is under judicial procedure of the **state medical council**.
- The basic principle related to medical negligence is known as '**Bolam Rule**'.

Defenses against negligence

- No duty owed to the plaintiff (patient); i.e. no doctor-patient relationship established.
- Duty discharged according to prevailing standards
- Therapeutic Misadventure
- Error of judgment
- Medical maloccurrence
- Informed consent for the act was taken
- Patient was guilty of contributory negligence in
- **Res judicata**, i.e. if a question of negligence against a doctor has already been decided by a court the patient cannot contest the same in another proceeding. Only appeal can be made.
- **Res Indicato** (Limitation): The case should be **filed within 2 years of alleged negligence**.

CONSENT

- A child **under 12 years cannot** give valid consent to suffer any harm which may result from an act done in good faith and for its benefit. The consent of parent or guardian is taken (**Sec 89, IPC**).
- **Loco parentis**: Consent in place of parents by **person in charge of child**.
- A person **above 18 years can give consent to suffer any harm** which may result from an act not intended or not known to cause death or grievous hurt. (**Sec 87, IPC**).
- For **sterilization, hysterectomy and artificial insemination**, consent of **BOTH** partners is required.
- **Rules of Consent**—informed consent has 5 essential components:
 - **Disclosure**: Patient must be told **nature of his disease**; **option/alternatives** available; **costs** involved; **success/failure** rates; **prognosis**; **IF SURGERY-local/general anesthesia**; **risks of anesthesia**; **possible operative procedures and risk/benefits of each**.
 - **Comprehension**: Consent should be taken in a **language that patient can understand**; if necessary an interpreter may be used.
 - **Absence of any outside control over the decision**: **No pressure** should be applied by the doctor, nurse or paramedical personnel.
 - **Competence**: Patient should be **above age of 12 years** (for GPI) and **above age of 18 years** (for surgery);

should be mentally sound and should not be under the influence of alcohol or drugs.

➤ **Actual consent:** should be **written**; **signature of patient** obtained and signature of two independent **witnesses** obtained.

• **Exceptions to informed consent**

- Emergencies
- Therapeutic privilege
- Therapeutic waiver
- Medicolegal postmortems
- Examination of convicts
- Attempted suicide

MEDICAL COUNCIL OF INDIA (MCI)

MCI Act

- **Schedule 1** of MCI act: Degrees awarded by **Indian universities**.
- **Schedule 2:** Degrees awarded by **Foreign universities**.
- **Schedule 3:** Part 1—recognized degrees other than MBBS (LMP, CPS diploma); part 2—recognized degrees other than MBBS awarded by foreign boards.

MCI Rules for Medical Records Maintenance

- As per MCI, **medical records of inpatients** should be **maintained for 3 years** from the date of commencement of the treatment.
- If any request is made for medical records either by the patients/authorised attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of **72 hours**.
- A registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate he/she shall always enter the identification marks of the patient and keep a copy of the certificate. He/She shall not omit to record the signature and/or thumb mark, address and at least one identification mark of the patient on the medical certificates or report.

Terms

- **Medical etiquette:** Refers to the conventional laws of courtesy observed between members of the medical profession.
- **Medical ethics:** Is the study of moral principles guiding medical men in their dealings with their patients.
- **Medical jurisprudence:** Is the study of legal principles that guide medical personnel.

- **Declaration of Geneva** (adopted by World Medical Association in 1948) is an ethical modification of the hippocratic oath, last modified in 2006.

IDENTIFICATION

- **The Corpus Delicti** – (the **body of offence, essence of crime**) means the contributing factors (body, bullet, weapon, etc.) of any predefined criminal offence, e.g. murder. It must be proven that a crime has occurred before a person can be convicted of committing the crime. The main part of corpus delicti is **establishment of identity** of dead body.

Race Determination of Skeleton

Cephalic Index	Type of Skull	Race
70–75	Dolicho-Cephalic (Long heads)	Pure Aryans Aborigines, Negros
75–80	Mesati-Cephalic (medium headed)	(Indians), Europeans and Chinese
80–85	Brachy-cephalic (Short headed)	Mongolian
85–89.9	Hyperbrachy-cephalic (very round or broad head)	Apert syndrome

- **Cephalic index** = Max breadth of skull/Max length of skull × 100
- **Crural Index** = Length of tibia/Length of femur × 100
- **Brachial Index** = Length of radius/Length of humerus × 100
- **Humero-femoral index** = Length of humerus/Length of femur × 100
- **Intermembral Index** = (Length of humerus + radius)/(Length of femur + tibia) × 100

Feature	Caucasians	Mongols	Negros
Orbit	Triangular	Small round	Square
Nasal Opening	Narrow elongated	Rounded	Broad
Palate	Triangular	Rounded or horseshoe shaped	Rectangular
Face	Orthognathism (straight lower face)	Large and flattened malar bones	Prognathism (jaw projecting)

Sex Determination

- Sex from chromatin can be determined by **Barr body**, **Davidson Smith body**, **Feulgen reaction**, **Quinacrine staining**.

- **Barr body** is the single inactive X chromosome at the edge of nucleus found in the somatic cells of most females (XX). Number of Barr bodies is one less than the number of X chromosomes, i.e. **NO** barr body in normal male (XY) and Turner's syndrome (XO); **ONE** Barr body in Klinefelters syndrome (XXY) and **TWO** Barr bodies in super-female (XXX).

- **Davidson body**— in polymorphonuclear leucocytes (neutrophils) of **females**, there is a **drumstick** like projection from the lobe of the nucleus.

- Important bones used for sex determination are: **pelvis, skull, mandible, vertebra, femur** and **scapula**.

- In the skeleton the **best criteria** for determining sex are in the **pelvic bones**— especially **sciatic notch index**.

- According to **Krogman**, the degree of accuracy in sexing adult skeletal remains is

- Entire skeleton : **100%**
- Pelvis + skull : **98%**
- Pelvis only : **95%**
- Skull only : **90%**
- Long bones only : **80%**

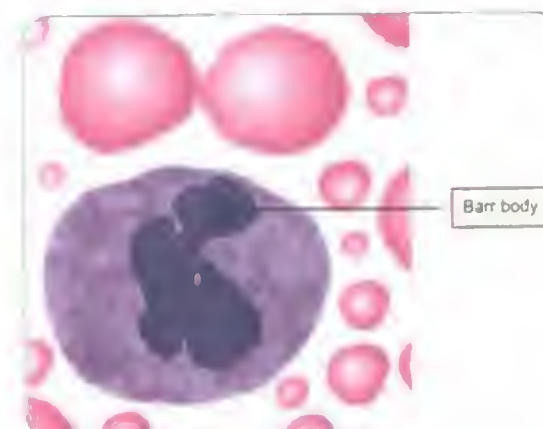


Fig. 15.1: Barr body in buccal epithelium

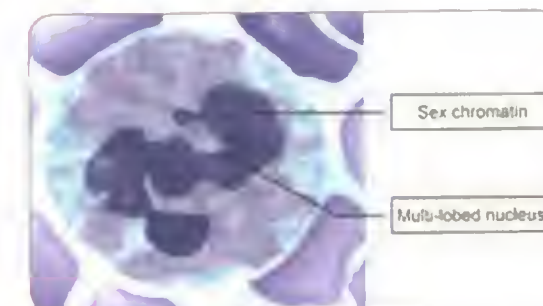


Fig. 15.2: Davidson body (drumstick appearance) in neutrophil

	Male	Female
Skull		
Skull capacity	1500–1550 mL	1350–1400 mL
Orbits	Square	Rounded
Frontal eminences	Small	Large
Occipital area	Muscle lines and protuberances prominent	Not prominent
Chin	Square (U shaped)	Round
Mandible		
Ascending ramus of mandible	Greater breadth	Small breadth
Angle of body and ramus (gonion)	Less obtuse and everted	More obtuse and inverted
Hip Bone		
Preauricular sulcus (attachment of anterior sacroiliac ligament)	Not frequent, narrow, shallow	More frequent, broad and deep
Ischial tuberosity	Inverted	Everted, more widely separated
Iliopectineal line	Well marked and rough	Round and smooth
Greater sciatic notch	Smaller, narrower, deeper	Large, wide, shallow
Obturator foramen	Large, oval with base upwards	Small triangular with apex forwards
Subpubic angle	V shaped, sharp angle (70–75°)	U-shaped, rounded, broader angle (90–100°)
Pelvic brim or inlet	Heart-shaped	Circular or elliptical, more spacious, diameters longer
Pelvic cavity	Conical and funnel shaped	Broad and round
Washburn/ Ischiopubic Index (Pubic length in mm/ischial length in mm X 100)	73–94	91–111
Corporobasal Index (breadth of first sacral vertebra/breadth of base of sacrum X 100)	45	40.5

Contd

should be mentally sound and should not be under the influence of alcohol or drugs.

➤ **Actual consent:** should be **written**; **signature of patient** obtained and signature of two independent **witnesses** obtained.

• **Exceptions to informed consent**

- Emergencies
- Therapeutic privilege
- Therapeutic waiver
- Medicolegal postmortems
- Examination of convicts
- Attempted suicide

MEDICAL COUNCIL OF INDIA (MCI)

MCI Act

- **Schedule 1** of MCI act: Degrees awarded by **Indian universities**.
- **Schedule 2:** Degrees awarded by **Foreign universities**.
- **Schedule 3:** Part 1—recognized degrees other than MBBS (LMP, CPS diploma); part 2—recognized degrees other than MBBS awarded by foreign boards.

MCI Rules for Medical Records Maintenance

- As per MCI, **medical records of inpatients** should be **maintained for 3 years** from the date of commencement of the treatment.
- If any request is made for medical records either by the patients/authorised attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of **72 hours**.
- A registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate he/she shall always enter the identification marks of the patient and keep a copy of the certificate. He/She shall not omit to record the signature and/or thumb mark, address and at least one identification mark of the patient on the medical certificates or report.

Terms

- **Medical etiquette:** Refers to the conventional laws of courtesy observed between members of the medical profession.
- **Medical ethics:** Is the study of moral principles guiding medical men in their dealings with their patients.
- **Medical jurisprudence:** Is the study of legal principles that guide medical personnel.

- **Declaration of Geneva** (adopted by World Medical Association in 1948) is an ethical modification of the hippocratic oath, last modified in 2006.

IDENTIFICATION

- **The Corpus Delicti** – (the **body of offence, essence of crime**) means the contributing factors (body, bullet, weapon, etc.) of any predefined criminal offence, e.g. murder. It must be proven that a crime has occurred before a person can be convicted of committing the crime. The main part of corpus delicti is **establishment of identity** of dead body.

Race Determination of Skeleton

Cephalic Index	Type of Skull	Race
70–75	Dolico-Cephalic (Long heads)	Pure Aryans Aborigines Negros
75–80	Mesati-Cephalic (medium headed)	(Indians), Europeans and Chinese
80–85	Brachy-cephalic (Short headed)	Mongolian
85–89.9	Hyperbrachy-cephalic (very round or broad head)	Apert syndrome

- **Cephalic index** = Max breadth of skull/Max length of skull × 100
- **Crural Index** = Length of tibia/Length of femur × 100
- **Brachial Index** = Length of radius/Length of humerus × 100
- **Humero-femoral index** = Length of humerus/Length of femur × 100
- **Intermembral Index** = (Length of humerus + radius)/(Length of femur + tibia) × 100

Feature	Caucasians	Mongols	Negros
Orbit	Triangular	Small round	Square
Nasal Opening	Narrow elongated	Rounded	Broad
Palate	Triangular	Rounded or horseshoe shaped	Rectangular
Face	Orthognathism (straight lower face)	Large and flattened malar bones	Prognathism (jaw projecting)

Sex Determination

- Sex from chromatin can be determined by **Barr body**, **Davidson Smith body**, **Feulgen reaction**, **Quinacrine staining**.

- **Barr body** is the single inactive X chromosome at the edge of nucleus found in the somatic cells of most females (XX). Number of Barr bodies is one less than the number of X chromosomes, i.e. **NO** barr body in normal male (XY) and Turner's syndrome (XO); **ONE** Barr body in Klinefelters syndrome (XXY) and **TWO** Barr bodies in super-female (XXX).

- **Davidson body**— in polymorphonuclear leucocytes (neutrophils) of **females**, there is a **drumstick** like projection from the lobe of the nucleus.

- Important bones used for sex determination are: **pelvis, skull, mandible, vertebra, femur** and **scapula**.

- In the skeleton the **best criteria** for determining sex are in the **pelvic bones**— especially **sciatic notch index**.

- According to **Krogman**, the degree of accuracy in sexing adult skeletal remains is

- Entire skeleton : **100%**
- Pelvis + skull : **98%**
- Pelvis only : **95%**
- Skull only : **90%**
- Long bones only : **80%**

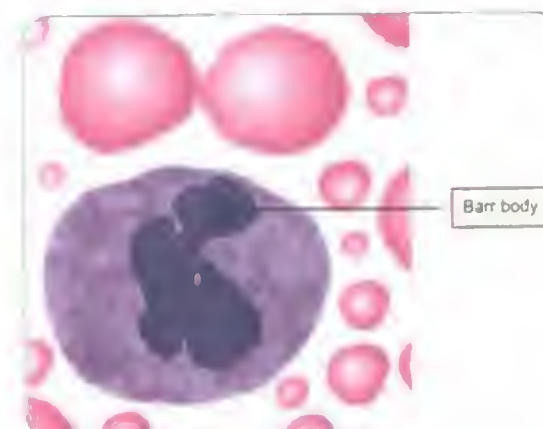


Fig. 15.1: Barr body in buccal epithelium

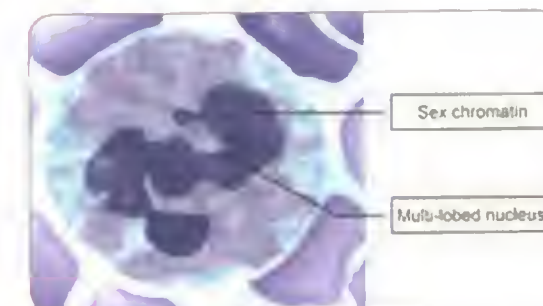


Fig. 15.2: Davidson body (drumstick appearance) in neutrophil

	Male	Female
Skull		
Skull capacity	1500–1550 mL	1350–1400 mL
Orbits	Square	Rounded
Frontal eminences	Small	Large
Occipital area	Muscle lines and protuberances prominent	Not prominent
Chin	Square (U shaped)	Round
Mandible		
Ascending ramus of mandible	Greater breadth	Small breadth
Angle of body and ramus (gonion)	Less obtuse and everted	More obtuse and inverted
Hip Bone		
Preauricular sulcus (attachment of anterior sacroiliac ligament)	Not frequent, narrow, shallow	More frequent, broad and deep
Ischial tuberosity	Inverted	Everted, more widely separated
Iliopectineal line	Well marked and rough	Round and smooth
Greater sciatic notch	Smaller, narrower, deeper	Large, wide, shallow
Obturator foramen	Large, oval with base upwards	Small triangular with apex forwards
Subpubic angle	V shaped, sharp angle (70–75°)	U-shaped, rounded, broader angle (90–100°)
Pelvic brim or inlet	Heart-shaped	Circular or elliptical, more spacious, diameters longer
Pelvic cavity	Conical and funnel shaped	Broad and round
Washburn/ Ischiopubic Index (Pubic length in mm/ischial length in mm X 100)	73–94	91–111
Corporobasal Index (breadth of first sacral vertebra/breadth of base of sacrum X 100)	45	40.5

Contd

Cond.

	Male	Female
Hip Bone		
Kimura's base wing index (Alar Index) (width of wing/breadth of 1st sacral vertebra X 100)	65	80
Sternum		
Ashley's rule of 149	Total length > 149 mm	Total length < 149 mm
Hyrtl's law	Body is longer and more than twice the length of the manubrium	Body is shorter and less than twice the length of the manubrium
Sternal Index (length of manubrium/length of body X 100)	46.2	54.3
Sternal foramen	More common	Less common

Indices Used for Determination of Sex

Index	Sex determination from
Sternal index and Ashley's rule	Sternum
Ischlopubic and Sciatic notch Index	Hip bone
Kimura's (alar) index and Corporobasal index	Sacrum
Medullary index	Long bones
Chilotic line index (pelvic segment predominant in females; sacral segment in males)	Sacrum/pelvis

TEETH (FORENSIC ODONTOLOGY)

Temporary and Permanent Teeth

- Temporary teeth** (Deciduous/Milk teeth): Dental formula is 2 Incisors + 1 Canine + 0 Premolar + 2 Molar = 5 in each quadrant (2102/2102). So total $5 \times 4 = 20$ temporary teeth.
- Permanent teeth**: Dental formula is 2 Incisors + 1 Canine + 2 Premolars + 3 Molars = 8 in each quadrant. (2123/2123). So total $8 \times 4 = 32$ permanent teeth.

Eruption of permanent teeth	Mnemonic
First Molars (6–7 years)	Mummy
Central Incisors (6–8 years)	Is
Lateral Incisors (7–9 years)	In
First Premolar (9–11 years)	Pain
Second Premolar (10–12 years)	Papa
Canines (11–12 years)	Can
Second Molars (12–14 years)	Make
Third Molars (17–25 years)	Medicine

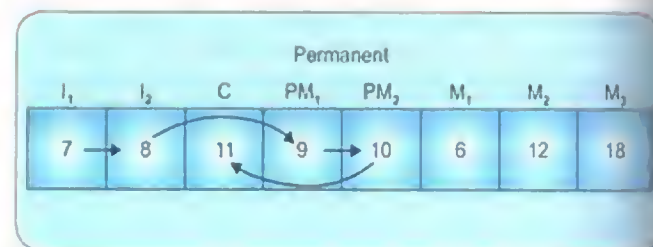


Fig. 15.3: Visual mnemonic for eruption of permanent teeth

- The above figure is a visual mnemonic for time of eruption of permanent teeth. (i) Draw all 8 permanent teeth in the form of a table. (ii) First fill up ages of eruption of molars which are a table of 6 (6, 12 and 18 years). (iii) Now fill up ages for rest of the teeth appearing from medial to lateral with a gap of 1 year except canine which appears at 11 years.
- At two and half years, the 20 temporary teeth should have erupted.
- In both deciduous and permanent teeth *dentition occurs earlier in Lower jaw* and on *Left side*.
- 1st deciduous teeth/temporary teeth to erupt** is **lower central incisor, left**.
- 1st permanent teeth to erupt** are **lower first molars**.
- Tooth eruption may be **earlier in girls** by 1 year.

Age Estimation by Teeth

- Gustafson's method**: The (postmortem) age estimation of adult over 25 years depends on the physiologic changes in each of the dental tissues. **Transparency of root** is the most reliable of all criteria—seen after 30 years of age.
- Other methods of age estimation by using teeth:
 - **Lamendin** (parodontal disease and transparency of root)
 - **Boyde** (incremental lines method)

- **Stack's method** (height and weight of erupting teeth—used for infants)
- **Miles** (changes of root transparency) method.

More 'Teeth' Points

- In *ante mortem* tooth loss or extraction the bony rim of the alveolus is **sharp and feathered**.
- MC tooth to be impacted** is **lower 3rd molar**.
- Wisdom tooth** is third molar. It is **most erratic in its eruption** and is of little value in determining age.
- Oroental/Oroantral fistula** are common after extraction of **1st molar tooth**.
- Hutchinson's teeth** (upper peg shaped incisors) and mulberry molar/moon's molars are seen in **congenital syphilis**.

Race from the Teeth

- Size of tooth:
 - **Indians**: **small** teeth
 - **Australian Aborigines**: **large** teeth
- Cusp: Extra cusps (6–7 in number!) in molar teeth—Americans > Indians
- Shape:
 - **Mongoloid**: **Shovel** shaped incisors
 - **Europeans**: **Peg** shaped lateral incisors
- Surface: Almost 100% of **Europeans** have a flat lingual surface of incisor teeth
- Ridges: **Japanese and Mongoloid** have ridges in lingual surface of teeth
- Root: In Mongoloids, lower molars have **three roots**
- Appearance: Regarding, the occlusal surface of first molar
 - **Caucasians**: It is larger and more tapered
 - **Negro**: Small and square shaped
 - **Mongoloid**: **Large and rounded**
- Crazy Mnemonic for **Mongoloid** from above facts: 'Imagine a **large and round** Mongoloid fellow carrying a **shovel** in his hand for digging up a tree with **three roots**!'

Dental (tooth) Numbering systems

- Zsigmondy – Palmer system
- Universal system (ADA system)
- FDI system (Federation Dentaire Internationale)
- Haderup system

1. Universal System:

Right	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Left
	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	

2. Palmer's notation:

Right	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	Left
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	

3. Haderup system:

Right	8+7+6+5+4+3+2+1+	+1+2+3+4+5+6+7+8	Left
	8-7-6-5-4-3-2-1-	-1-2-3-4-5-6-7-8	

4. FDI (Federation Dentaire Internationale) Two Digit System:

Right	1	2	Left
	4	3	

5. Modified FDI System:

Right	1	2	Left
	3	4	

Fig. 15.4: Dental numbering systems

STATURE

- Anthropometry** is also called **Bertillon system**.
- Humerus length** is **1/5th (20%)**; **tibia** is **22%**; **femur** is **27%** and spine is 35% of the individual's height.
- Length of long bone is measured by **osteometric board**.
- It is then multiplied by a factor to obtain the stature according to **Pearson's formula** and Trotter's and Glessers formula.
- Rule of Haase and Morrison's rule**: These are rough methods of calculating the age of the fetus based on fetal length.
- Rule of Haase**: During the first five months of pregnancy the square root of the length gives the approx age of the fetus in months. During last five months the length in centimeters is divided by five gives the age in months.
- Determination of stature from long bones is by the following formulae: **Karl Pearson's**; **Trotter and Gleser's**; **Dupertius** and **Hadden**; and **Breitinger's formula**.

HAIR

Feature	Human hair	Animal hair
External	Delicate, fine and thin	Coarse and thick

Contd

Contd.

Feature	Human hair	Animal hair
Color	Black, grey, reddish or reddish brown	Any color, can have banded appearance
Shaft diameter	50–150 microns	25 microns or > 3000 microns
Root	Bulb or ribbon shaped	Brush like
Tip	Cut or frayed (scalp hair)	Tapered
Cuticular scales	Short, broad, thin and irregularly annular	Large and have step-like or wavy projections
Cortex	Thick, well striated, 4-10 times as broad as medulla	Thin
Medulla	Narrow, may be continuous, interrupted, fragmented or even absent	Broad, continuous and always present
Medullary index	< 1/3	> 1/3
Pigment granules	Uniformly distributed	Mostly clumped near the medulla
Precipitin test (with intact root)	Specific for human	Specific for animal

More Hair One-Liners

- **Trichology** = Study of hair.
- **Medullary Index** = Diameter of medulla/Diameter of cortex.
- Human hair has thin nonpigmented **scales**.
- **Negroes have wooly hair of fragmented type**.
- **Animal hairs** are coarse and thick; thin cortex; large scales and wide medullary index.
- **Barr bodies** can be detected in the hair follicles in about 20-80% of females and only about 0-4% males.

- **Blood groups (ABO)** can be determined from a single hair bulb.
- **Post-mortem root banding** seen in people who are dead for some time wherein an opaque band of 0.5 mm above the root bulb can be observed with transmitted light microscope.
- **Singeing of hair** indicates burns or close firearm injury.
- **Time since death** can be calculated from the growth of scalp hair and beard (2.5 mm/week or 0.4 mm/day).
- Hair is brittle, singed or charred with large and round vacuoles at the point of burning which is **absent in scalds**.
- **Poison** can be detected from hair, **arsenic, thallium and lead**.

FINGERPRINTING (DACTYLOGRAPHY, GALTON SYSTEM, DERMATOGLYPHICS)

- Fingerprint systems is also known as **dactylography Galton system** or **dermatoglyphics**.
- **First fingerprinting bureau** of the world was established in **Kolkata, India in 1897**.
- Fingerprints are formed during **intrauterine life**.
- Fingerprints are the **best identification system** till date (dental status is second best).
- **MC** fingerprint pattern is **Loops (67%) > whorls > arch > composite**.
- Fingerprint pattern is different even in **identical (monozygotic) twins**.
- **Quelet rule** of biological variation: 'All nature made things have unlimited and infinite forms of variations'; the chance of two persons having identical fingerprints is about **1 in 64 thousand million**.
- Generally **16-20 points** of comparison are accepted as proof of identity.
- Fingerprints are recorded on **unglazed white paper** using **printer's ink**; before taking prints, hands are **washed and dried**.

Medicolegal importance of various age groups

Age	Medicolegal importance
3rd lunar month (12 weeks of pregnancy)	Till this duration, decision for termination of pregnancy can be taken by one doctor.
5th lunar month (20 weeks of pregnancy)	Maximum period of gestation for use of the Indication of MTP Act. Above this age, termination is only on therapeutic grounds.
7th lunar month (28 weeks of pregnancy)	Fetus born after this period, if it does not show any sign of life, is termed stillborn fetus.
7th calendar month (210 days)	Fetus is considered to be viable.
10th lunar month	Fetus at this stage is a full term fetus.

Contd.,

Contd.

Age	Medicolegal importance
5 years ¹⁴	Above this age, a child becomes responsible for his act leading to wreckage of train (according to Railway Act).
7 years ¹⁵	Below this age, child is not responsible for his criminal act, as he does not understand the nature and consequences of his act (Sec. 82 IPC).
7-12 years	Criminal responsibility: A child may or may not be held responsible for his act by the court, depending upon whether the child has attained sufficient maturity to understand the nature and consequence of the act (Sec. 83 IPC).
10 years	If a child below this age is removed from his lawful guardian for purpose of robbing movable property from his/her possession, it will amount to kidnapping (Sec. 369 IPC) .
12 years	A child under 12 years cannot give valid consent to suffer any harm which may occur from any act done in good faith and for his benefit (Sec. 89 IPC).
14 years	Employment: According to the Factory Act, a person below this age is a child and cannot be employed in factory jobs.
14-15 years	A person can be engaged in non-hazardous factory jobs for a limited period during the day hours.
15 years	<ul style="list-style-type: none">• Sexual Intercourse even with wife, below this age amounts to rape.• A person above 15 years of age can be employed in a factory like an adult, if he has a fitness certificate from a doctor.
16 years	<ul style="list-style-type: none">• Taking away a male under this age without consent of guardian amounts to kidnapping.• Statutory rape: Intercourse with a girl below this age, irrespective of whether with or without her consent amounts to rape.
17 years	<ul style="list-style-type: none">• Admission in a medical college.• A juvenile or child over this age but < 18 years, would stay in the after-care organization till he attains the age of 20 years.
18 years	<ul style="list-style-type: none">• Judicial punishment: Below this age, an offender is juvenile and is tried in juvenile court and if convicted, sent to reformatory school (no imprisonment or death sentence).• Age of majority except when the individual is under guardianship of court.• Age of marriage for females.• Can cast vote.• Mentally sound person can make a valid will.• Taking out or enticement of a girl below this age from custody of her guardian amounts to kidnapping.• Kidnapping a boy or girl below this age for purpose of begging is punishable with imprisonment of 10 years with or without fine.• Can be employed in any authorized job in a factory.• Can give valid consent to suffer any harm which may result from an act not intended or not known to cause death or grievous hurt (Sec. 87 IPC).• Minimum age for entering a government service.
21 years	<ul style="list-style-type: none">• Age of marriage for males.• If a girl below this age is 'imported' to India from foreign country for the purpose of illicit intercourse, the act amounts to kidnapping (Sec. 366 B IPC).• Person under the guardianship of the Court of Wards attains majority.
25 years	<ul style="list-style-type: none">• Age for contesting membership of parliament and other legislative bodies.• Age limit for entering in some government services.• According to Punjab Excise Act, a person below this age cannot buy and consume liquor.
45 years	Minimum age for appointment as President, Vice-President and Governor of States in India.
55-65 years	Age of retirement from services under the government, Statutory bodies, autonomous bodies/institutes or from judiciary services.

- Methods used to develop fingerprints: aluminum dust (grey powder); charcoal powder (black powder); iodine vapor and ninhydrin solution.
- 'FINDER'—FINGERprint reader, a computerized method of fingerprint maintenance; used by FBI; 8 fingers (excluding little fingers) are scanned.
- In 'Pigeonhole' method, all 10 fingers are recorded.
- **Parascopy** is the further study of fingerprints (pores on the ridges of fingers and hand) described by Edmond Locard.
- **Permanent Impairment** of fingerprints occurs in **leprosy; electrical injury** and **radiation injury**.
- **Temporary** modification may occur in **celiac disease**.
- Distance between ridges may change BUT pattern not change in **rickets** and **acromegaly**.
- **Thumb** Impression, is taken from **left thumb for males** and **right thumb for females** ('If you are married/have a girlfriend, you will know this—females are always right!').



Fig. 15.5: Different fingerprint patterns
Courtesy: Dr Vipul Ambade

Tattooing

- Tattoo mark is permanent when dye penetrates the **dermis**.
- Tattoo marks are recognized **even** in decomposed bodies.
- **Dyes** commonly used in tattooing are:
 - **Black color:** India Ink (**MC used**); China Ink, Soot
 - **Blue:** Prussian blue (ferric ferrocyanide); Cobalt, Indigo, Ultramarine

Tattooing

- **Green:** Chromic oxide
- **Red:** Cinnabar, vermilion
- **Brown:** Ochre
- **Methods to make tattoo readily visible are:**
 - **Infrared** photography
 - **Ultraviolet** light
 - Rubbing the part and examining under magnifying glass
 - Treating with **hydrogen peroxide** and **0.5% caustic potash**
 - Histological examination of **regional lymph nodes** may show tattoo pigment deposition.

Other High Yield Facts

- Lip prints = **Chelloscopy**.
- **Palatoprints/Rugoscopy:** study of pattern of rugae present on **anterior part of hard palate**.
- **Superimposition** is technique applied to determine whether the **skull** is that of the person in the photograph.
- The amino acid content of bones falls gradually (detected by **thin layer chromatography**). Analysis of **fresh bones may yield 15 amino acids** whereas **bones that are a 100 or more years old may yield only 7**.
- **Galstaun** studied the appearance and fusion of ossification centers in Bengali population in 1937. As per Galstaun's method, iliac crest fuses in females at the age of **17–19 years**.
- As per **Delhi Anatomy Act**, the police is legally authorized to dispose off the dead body if the body is unclaimed for **72 hours**.

Note

- **Lunar month—28 days, calendar month—30 days**

POSTMORTEM CHANGES

Certification of Brain Death

- According to Transplantation of Human Organs Act, four doctors are authorised to certify brain death.
 1. **RMP in charge of the hospital** in which brainstem death occurred.
 2. **RMP** (physician, surgeon or intensivist) **nominated** from the panel of names approved by appropriate authority.
 3. **Neurologist/neurosurgeon** nominated as above.
 4. **RMP** (including **duty doctor**) **treating** the aforesaid person.
- **Thanatology:** The study of death in all its aspects.

Somatic Death (systemic death or clinical death).

- It is the complete and irreversible stoppage of circulation, respiration and brain functions (**Bishop's tripod of life**).

Clinical criteria for brain death:

- ▶ **Coma**
- ▶ **Absence of brainstem reflexes:** Pupillary reflex; oculo-vestibular reflex; corneal reflex, pharyngeal and tracheal and gag reflexes
- ▶ **Apnea:** pulse rate invariant and unresponsive to atropine.

Molecular death (cellular death) refers to death of all individual cells.

Suspended Animation

- In this condition **no signs of life** are discovered as the functions are interrupted for some time—**apparent death** BUT NO somatic death, brain death or molecular death. **Resuscitation is successful** in such cases.
- Seen in: **Newborn infants; drowning; electrocution; Yagis; cholera;** after anesthesia; typhoid state; shock; anastroke; cerebral concussion; insanity etc.

EXTRA EDGE

- **Harvard criteria** is for 'brain death'. ECG is mandatory. Check respiration for 3 minutes. Repeat test after 24 hours.
- **Minnesota criteria** is for 'brainstem death'. ECG is not mandatory check respiration for 4 minutes. Repeat test after 12 hours.

Immediate signs of death

1. **Permanent cessation of lung function**
 - Feather test:** Feather held in front of nose does not move
 - Mirror test:** Mirror held in front of nose does not show fogging
 - Winslow test:** No movement of water kept in bowl on the chest.
2. **Permanent cessation of heart and flat ECG (these test check patency of circulation)**
 - Magnus test (ligature test):** Fingers do not swell or get congested when ligature applied to its base
 - Diaphanous test (transillumination test):** Failure to show redness in finger webspace when transilluminated from behind
 - Isard test:** Failure to show yellowish brown discoloration of skin on injection of fluorescein dye.

Other Early Signs of Death

Ocular Signs

- **Tache noire de sclerotica** ('black spot'): is a **dark, reddish brown strip** that will **form horizontally across the eye ball**;

occur when **eyelids are open postmortem**; if the individual drowned, or the body was found **in water, the tache noire is absent**. Usually appears **within 3 hours of death**.

- Increase in **potassium level in vitreous humor** - used for determining time of death.
- Fragmentation or segmentation (trucking or shunting) of the blood columns in the retinal vessels (**Kevorkian sign**) appear within minutes after death, and persists for about an hour.



Fig. 15.6: Tache noire

Algor mortis

- Refers to **cooling of the body** ('chill of death')
- In tropical climates/India the heat loss is roughly **0.5–0.7°C**/hour and body attains atmospheric temperature by **16–20 hours**.
- **MC site** for recording temperature is the **rectum**
- **Time since death** may be determined
- Cooling curve is **sigmoid shaped**

Postmortem caloricity

- Temperature of the body remains **raised for the first 2 hours after death**
- Occurs in **tetanus; strychnine poisoning; septicemic candidia; cholera, pontine hemorrhage; sunstroke (heatstroke), other fevers**

Cadaveric spasm

- **Instantaneous rigor, death clutch, cataleptic rigidity** is a condition wherein stiffening occurs in a **single group of voluntary muscles**, which were already in a state of contraction at the time of death (**no primary relaxation**). It indicates **mode of death** (ex: grass weeds in hand—drowning, suicide—weapon in hand)—indicates **emotional/physical activity** at time of death.



Fig. 15.7: Cadaveric spasm

Rigor Mortis (RM)

- It is also known as cadaveric rigidity (NOT spasm!)
- Contraction, stiffening, shortening and opacification** of muscles after death.
- Occurs due to **ATP depletion**; it occurs after **molecular death**; stage of **primary relaxation** exists.
- Appears first in involuntary muscles of heart**; then it begins in the **eyelids** >> neck >> lower jaw >> muscle of face >> muscle of chest and UL >> abdomen >> LL muscle - **proximal-distal order** — called **Nysten's law**.
- Indicates **time of death**.
- Time of onset of RM— In India it begins in **1 to 2 hours after death** and takes further 1 to 2 hours to develop.
- Duration of RM - In India it lasts usually **24 to 48 hours in winter and 18 to 36 hours in summer**. It lasts for 2 to 3 days in temperate regions.
- RM does NOT OCCUR in a **fetus of less than 7 months**.

Early onset RM	Delayed onset RM
Occurs in death due to	Occurs in death due to
• Strychnine poisoning	• Arsenic poisoning (lasts longer also)
• Diseases: cholera, cancer, TB, typhoid	• Apoplexy
• Fatigue/exhaustion before death (due to rapid ATP depletion).	• Pneumonia
	• Asphyxia

Fig. 15.8: Rigor mortis
Courtesy: Dr Mukund Jadhav

Putrefaction/Decomposition

- This is the **final stage following death** produced by the **action of bacterial enzymes**, mostly **anaerobic organisms** derived from the bowel. Due to putrefaction inner vessel walls stain purplish red giving '**marbled appearance**' (occurs in **24–48 hours**).
- The **first external sign** of putrefaction in a body lying in air is usually a **greenish discoloration of skin over the region of the caecum (right iliac fossa)**. Color is due to **sulphmethemoglobin**.
- The **first internal sign** of putrefaction is **raddish brown discoloration of inner surface of vessels (esp the aorta)**.
- Entomology: Maggots appear in 1-2 days after death** adult flies will be coming out of the body 8-12 days after death; this helps to determine the **time of death**.
- Liver becomes spongy and is called as **foamy liver or swiss cheese liver or honeycombed liver**.
- If body is in water, floatation of body occurs due to accumulation of putrefactive gases; time required for floatation is **24 hours after death in summers** and **2-3 days in winters**.
- Rate of putrefaction is maximum in **air > water > soil > earth**.
- First organ to putrefy** is larynx and trachea.
- Last organ to putrefy** in male is **prostate**; in female **virgin uterus**. Bone is the last structure.
- Casper's Dictum: Effect of the medium (in which the body lies)** in the rate of putrefaction; under the same environmental temperature, **one week of putrefaction in air** is equivalent to two weeks in water, which is equivalent to eight weeks buried in soil, **indicates time of death**.
- Pink teeth** may be seen in putrefaction due to extravasated **blood in dentinal tubules**.

Early putrefaction	Delayed putrefaction
• Death due to septicemia, peritonitis, asphyxia	• Death due to wasting disease, anemia, debility;
• Free access to air and lots of moisture	• Death due to poisoning by carbolic acid, zinc chloride, strychnine (nuxvomica) and chronic heavy metal poisoning.
	• Temperature < 0°C or > 48°C



Fig. 15.9: Marbling



Fig. 15.10: Greenish discoloration of right iliac fossa

Adipocere (Saponification, Grave Wax)

- This is a modification of putrefaction where fatty tissues of the body change to a substance known as **adipocere (in absence of air)**. This change is due to gradual **hydrolysis and hydrogenation** of **pre-existing fats**.
- Adipocere occurs in bodies immersed in **water** or **buried in damp clay soil or alkaline soil**.
- Adipocere **first starts in subcutaneous tissues**.
- Complete conversion to adipocere in an adult limb takes **3 to 6 months**.
- Adipocere does NOT OCCUR in fetus under 7 months of age.

Mummification

- Drying or dehydration/dessication** and **shrivelling** of the cadaver occurring due to **excess air and warmth (hot, dry climate)** with **lack of moisture (evaporation of water)**.
- A mummified body is practically **odorless**.
- It occurs in **shallow graves in dry sandy soil**.

Early mummification	Delayed mummification
Occurs in bodies buried in dry sandy soil, shallow graves , and in chronic arsenic or antimony poisoning	Occurs in moisture environment

Postmortem Lividity

- Synonyms: Postmortem Hypostasis, Livor Mortis, Postmortem staining, Vibices, Suggillations.**
- Bluish purple/purplish red discoloration** of **skin and internal organs** which appears under the skin of the **dependant parts of the body** due to **capillovenous distension**. Pressure points are **spared**.
- Not elevated; has sharply defined horizontal margins.
- It appears **1-3 hours after death**, is usually well developed within 4 hours and reaches a **maximum**

between 6 to 12 hours (fixation of postmortem staining); It ends when putrefaction sets in.

Color of hypostasis	Poisoning
Cherry Red	Carbon monoxide
Bright Red/Brick red or Pink	Hydrocyanic acid; potassium cyanide; cyanide; hypothermia; refrigerated bodies
Dark Brown (chocolate)	Phosphorus
Red Brown	Aniline, nitrates, potassium chlorate/bicarbonate, nitrobenzene
Deep blue	CO ₂ (aniline also as per some books)
Bluish green	Hydrogen sulfide (H ₂ S)
Black	Opium
Bronze	Clostridial sepsis



Fig. 15.11: Postmortem lividity present over posterior aspect of body (except at pressure points)

Embalming

- Treatment of the dead body with antiseptics and preservatives to **prevent putrefaction**.
- Produces **chemical stiffening** similar to rigor BUT rigor mortis does not develop
- Embalming fluid** contains **formalin** (formaldehyde) 60%; **methyl alcohol**; **phenol glycerin**, **oil of winter-green (eucalyptus oil)**; **eosin**, **water**, **sodium borate/citrate/chloride**.

AUTOPSY

Autopsy Techniques

Rokitansky	In situ dissection of organs (Ideal for infants)
Letulle (en masse)	Removal of organs in toto
Virchow	Organs are removed one by one , most widely used method; cranial cavity is exposed first
Gahn (en bloc)	Combo of the above two methods; removal of organs in regional and functional groups (cervical, abdominal, genitourinary)

Autopsy Points

- Autopsy is done for the whole body.
- Autopsy should be conducted only on the *written orders from the police or magistrate*.
- After autopsy, *body is handed over to the investigating police officer* or the authority that has conducted the inquest in that case.
- In mortuary *dead body should be stored at 4 deg C*; for longer durations it should be stored at minus 20°C.
- Body should *never be undressed* before the forensic doctor sees it.
- After completion of autopsy, *all viscera should be replaced in the body and the body should be well embalmed* to facilitate a second autopsy.
- Most preferred method for *approaching the spinal cord* is *posteriorly*.
- Blood sample is taken from the *femoral vein*; 30 mL of blood should be preserved.
- In *autopsy in fetus/infants*, *Beneke's technique* and *Baar's technique* is used to open the skull.
- Subendocardial hemorrhage* MC in *left ventricle*; seen in poisonings (*arsenic, phosphorus, antimony, mercury*); *viperbite, heat stroke, acute infections, traumatic asphyxia, death due to burns, electrocution, head injury, sudden hypotension*.
- Last organ* to be dissected during *autopsy in asphyxial deaths* is the *neck*.

Exhumation

- There is **NO TIME LIMIT** for exhumation in India.
- The body is exhumed only when there is a **written order** by the **First Class Magistrate (Executive)**.
- It is done **under supervision of medical officer and magistrate**.
- Whole procedure should be conducted and **completed in natural daylight**—hence should be **started early in the morning**.

ASPHYXIAL DEATHS

Hanging

Typical hanging

- Knot is placed at occipital region and ligature runs from the midline above the thyroid cartilage symmetrically on both sides of the neck.
- A form of *asphyxia* which is caused by suspension of the body by a ligature, the **constricting force, being the body weight**.
- Cause of death is **asphyxia + venous congestion**.

Atypical hanging

Knot is placed anywhere **other** than occipital region; **MC site of knot** is near one side of mastoid process or angle of mandible

Complete hanging

Body completely suspended in air

Partial hanging

The body is partially suspended, **weight of the head** acts as constricting force. Body in **sitting, kneeling or lying down posture** indicates **partial hanging**.

Judicial hanging

Causes **# dislocation of C2 and C3** vertebrae - **Hangman fracture**; placement of knot **below chin (submental)** supposed to be most effective

- Ligature mark**: Most **important and specific sign of death from hanging**. The mark **encircles the neck except for the place where the knot was located**. The mark is situated **above the level of thyroid cartilage**.
- 'La facies sympathetica'**: A condition seen in hanging. If the ligature knot presses on **cervical sympathetic chain**, the **eye on the same side may remain open and the pupil dilated**. It indicates **antemortem hanging**.
- Antemortem hanging**: **Saliva dribbling** at angle of mouth is a **sure sign** (This is due to increased salivation just before death due to the stimulation of the salivary glands by the ligature); **seminal emission** is also a sign.
- Amussat's sign**: **Intima of carotid arteries** show transverse split.
- Lynching**: Homicidal hanging in which a the suspect/enemy is **hanged by a rope from a tree by the mob** without a trial; was practiced by **whites in America against Negroes**.
- A-P compression fracture of hyoid** seen in hanging.

Ligature tension involved in hanging

- Tension of 2 kg: block jugular vein
- Tension of 4-5 kg: block carotid arteries
- Tension of 15 kg: blocks trachea
- Tension of 20 kg: block vertebral arteries

Strangulation

- A form of asphyxia which is caused from constriction of the neck by a **ligature without** suspending the body.
- Here the ligature mark **completely encircles the neck and is below the thyroid**.
- Face is congested and **cyanosed**.
- Bloody froth at nose** and mouth.
- Frank bleeding** present.
- Subcutaneous tissue under ligature mark is **ecchymosed**.

Common Methods of Homicidal Strangulation

- Strangulation by ligature (**horizontal ligature mark** is seen).

- Throttling or manual strangulation by both hands**: Death is due to **reflex cardiac arrest**; **Inward compression fracture (adduction type) of Hyoid bone** is MC in **throttling**; Also **fracture of thyroid cartilage, larynx and trachea** are more common; **Bruising/rapture of neck muscles** is common.
- Bansdola** (using **strong bamboo** or stick).
- Garroting** (Victim attacked from behind by **Spanish windlass**—used earlier as an **official method of execution in Spain**. A loop of thin string is thrown around the neck of the victim who is attacked unawares from his back; the ligature is the tightened with the help of two sticks tied at the free ends of the string so as to constrict the neck strongly; was also used by **thugs in India** in the past).



Fig. 15.12: Adduction type of hyoid fracture in throttling

- Mugging** (strangulation by holding the neck of the victim **in bend of elbow**).
- Burking** is a method of **homicidal smothering and traumatic asphyxia**.

Other High Yield

- Gagging**: Closure of mouth/nose by cloth which is tied around the head or from forcing a cloth into the mouth. This may obstruct pharynx or force base of tongue against pharynx.
- Café coronary**: A condition wherein a restaurant patron dies suddenly during his dinner, apparently due to a sudden heart attack. At autopsy a large piece of meat is found in the throat, death is due to **asphyxia (laryngeal obstruction)**.
- Indien spots** in asphyxia are **numerous petechial hemorrhages** where capillaries are poorly supported as in **subconjunctival tissues and under the pleural and pericardial membranes**.

- Sexual asphyxia (autoerotic asphyxia)** is a/w **masochism and transvestism**; sexual pleasure **increased by pressure on carotid vessels**; seen in **young men MC**.
- Suffocation**: Asphyxia due to deprivation of oxygen includes **smothering, gagging, overlaying, burking, choking, traumatic asphyxia, drowning and hanging by ligature**. Throttling is **NOT** a type of suffocation.
- Positional asphyxia**: Body is in 'Jack-Knife' position; body is in such a position that abdominal organs press upon the diaphragm from below upwards.

Atypical Drowning

Type	Cause of death
Dry Drowning (water does NOT enter lungs)	Laryngeal spasm
Secondary drowning (Post-immersion syndrome, delayed drowning)	Death occurs in half hour to 2 days due to secondary changes in lungs and electrolyte disturbances
Immersion syndrome (submersion, hydrocution)	Vagal inhibition due to cold water striking epigastrium

- Eyes show **dilated pupils**.
- A fine, white, lathery **froth** is seen at the mouth and nostrils—most **characteristic external signs** of drowning.
- Water is present in lungs and stomach (**most important internal finding**).
- Cutis Anserina** (Goose flesh)—Due to spasm of erector pili muscles.
- Weeds, sand, etc. may be firmly grasped in the hand due to **cadaveric spasm**.
- Washerwoman's hands**: In drowning the skin of the palm has a whitish sodden appearance.
- Hemorrhages present **subpleurally** are **Paltan's hemorrhages**.
- Temporal bone hemorrhages** may be seen. (Also seen in deaths due to hanging, head injury and CO poisoning).
- Gettler's test**—is due to alteration in blood, difference in **chloride** content of blood in right and left heart; in **fresh water drowning due to hemolysis, chloride content is decreased in left side of heart** and opposite in saltwater drowning; > 25% is significant.
- Diatoms** in drowning may be found in **brain and bones**. Presence of **diatoms in bone marrow is definite internal sign of antemortem drowning**; diatoms are **unicellular algae**; cell wall contains **silica** which **resists acid digestion**—so to extract diatoms **acid digestion technique** is used.
- MC cause of drowning in India** is **accidental**.



Fig. 15.13: Washerwoman's hand

Typical Drowning

Wet drowning (Due to water inhaled into lungs - *emphysema aquosum*); may be of two types as shown here.

	Fresh water drowning	Salt water drowning
Circulation	Hemodilution, hypernatremia, lysis of RBCs	Hemoconcentration, hypovolemia, shock, crenated RBCs
Electrolytes	↑K ⁺ , ↓Cl ⁻	↑Mg ⁺⁺ and Cl ⁻
Cause of death	Ventricular fibrillation	Asystole/cardiac standstill (Mg ⁺⁺)

REGIONAL INJURIES

Abrasion

- **Grazes** (sliding, scraping abrasion) are the **MC type of abrasion** — occurs due to **friction**.

- **Brush burn/gravel rash**: An abrasion caused by violent rubbing against a broad surface as in dragging over the ground.
- **Friction burn (scuff or brush abrasion)**: Occurs due to tangential contact with a smooth surface or when the skin is covered by clothing.
- **Pressure abrasions (crushing abrasions)**: Example is **ligature mark** in hanging/strangulation and **teethbite mark**.
- **Impact abrasions** (contact or imprint abrasions) caused by impact - ex- when a person is **knocked down by a car** — **pattern of radiator grille or headlight** may be seen.
- Impact abrasions and pressure abrasions causing pattern of object are called **patterned abrasions**.
- **Differential diagnosis of abrasions**:
 - **Ant bites (erosions)** can mimic abrasions BUT bite marks are seen and vital reaction is absent
 - Skin excoriation by excreta
 - Pressure sores
 - Drying of skin of scrotum.
- Features of **post-mortem abrasion** (usually due to dragging the body):
 - Seen over bony prominences
 - Pale, dry and parchment like
 - NO scab; NO inflammation; NO microscopic changes

Age of Abrasion

- Fresh: Reddish, No scab
- 12-24 hrs: Dark red scab
- 1-2 days: Reddish brown scab
- 3-5 days: Dark brown scab
- 5-7 days: Blackish shrinking scab
- 7-10 days: Scab falls off leaving hypopigmentation

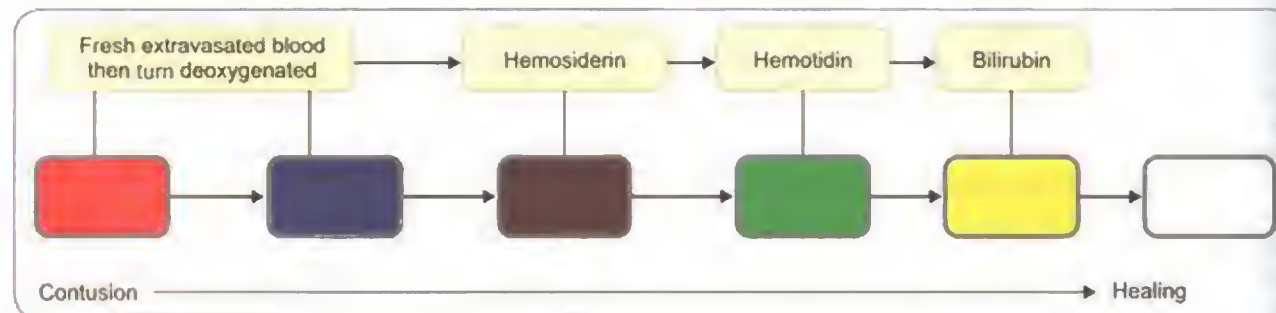


Fig. 15.14: Age of contusion — diagrammatic representation

Bruise (Contusion)

- **Bruise (contusion)** is an **extravasation of blood** into the tissues due to **rupture of subcutaneous vessels** due to trauma by **blunt object** (fist, lathi etc.). It is **lighter in color in areas of pressure; slightly raised with blurred margins**.
- **Ectopic bruise**: where the bruise occurs away from the site of impact - ex - **black eye** - due to # of floor of anterior cranial fossa or trauma to forehead.
- **Bruise occurs easily** on soft, loose and vascular parts such as **face, breast, vulva and scrotum**.
- NO contusion occurs on palms and soles.
- Bruising of **scalp is better felt than seen**.

Age of bruise (Fig. 15.14)

- At first: **Red (oxyhemoglobin)**
 - Few hrs to 3 days: **Blue (reduced hemoglobin)**
 - 4th day: **Bluish black (hemosiderin)**
 - 5-6 days: **Greenish (hematoidin)**
 - 7-12 days: **Yellow (bilirubin)**
 - 2 weeks: **Normal (absorption of pigment)**
- **Antemortem bruise**—will have **swelling; damage to epithelium; extravasation of tissue with blood and color changes; blurred margins**. Bruising usually **does NOT occur > 2 minutes after death** due to stoppage of circulation.
 - **Artificial bruise**: Juice of **marking nuts (semicarpus); calotropis or plumbago rosea** mimics bruise and is used for **false charges of assault**.
 - A blow with a **rod, a stick or a whip** produces two parallel linear hemorrhages (**railway line or tramline type**).
 - **Stomping** = Kicking and jumping on a person.
 - Blood localized in subcutaneous tissue appears blue on the surface due to light scattering processes in the dermis - **Rayleigh scattering**.
 - **Six-penny bruises** are discoid shaped about 1 cm in diameter and are due to **finger tip pressure** - seen in neck region in **manual strangulation** OR in the arms/forearms/wrist of a child in **battered baby syndrome**.
 - **Love bites ('hickeys')** are usually elliptical type of patterned bruise; caused due to a mixture of suction and application of tongue pressure; seen over neck, breasts and thighs. These are love bite marks caused during consensual lovemaking.

Laceration

- Lacerations are **splits/tears of skin, mucus membranes and underlying tissue**; hair and hair bulbs, nerve and **blood vessels are crushed** (so not much hemorrhage).

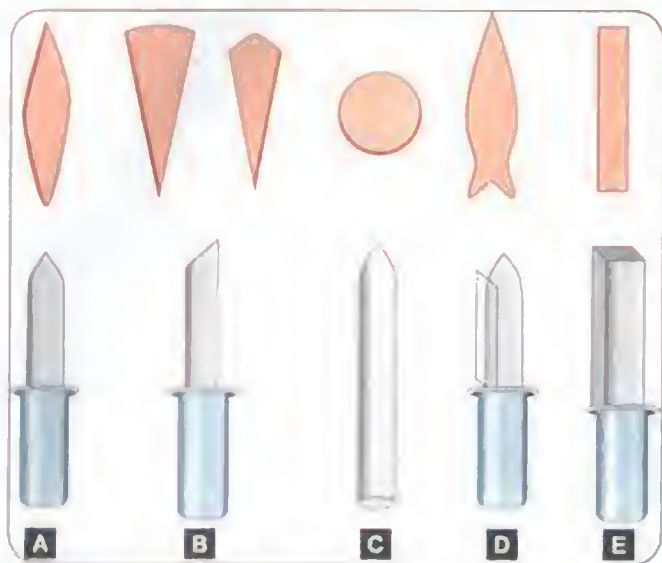
- **Split lacerations** — due to **blunt perpendicular impact; appears like incised wound**; esp on **scalp, eyebrow, zygomatic/cheek bone, iliac crest, tip of shoulder, shin, back of elbow**.
- **Avulsion**—due to **horizontal crushing impact; shearing laceration/flaying** — shearing force (such as lorry wheel) may cause separation of large area of skin.
- Tearing at the ends of lacerations are called '**swallow tails**'.

Incised Wound

- **Margins** are **well-defined, clean cut and everted**.
- **Length is greater** than its width; **width is greater than the edge of the weapon** causing it, due to retraction of divided tissues; Shape is usually **spindle shaped**.
- **Hemorrhage is usually more** as the vessels are cleanly cut.
- **Langer's lines of skin** determine **gaping of wound**; gaping is more when cut across Langer's lines.
- **Clean incised wounds** heal by **primary intention**.
- **Tentative Cuts/Hesitation marks** seen in **suicidal attempt injury**.
- **Defense wounds** indicate **homicide**.
- Incised wounds are deeper at their beginning since more pressure is exerted on the knife at this point - **head of the wound**; towards the end of the wound it becomes increasingly shallow - **tail of the wound**.
- **Postmortem wound clots**: **Red currant jelly** clots that are **NOT** attached to the underlying wall and there are **NO lines of Zahn (chicken fat appearance)**
- In **antemortem wound**, **wound serotonin and histamine content is more** and there is deep staining of the wound edges which can not be easily washed away.



Fig. 15.15: Healed scars of hesitation marks indicates suicide



Figs. 15.16A to E: Stab wound. A. Stab wound caused by blade with both edges sharp resulting in spindle shaped; B. Wedge shaped wound or tear drop wound if one edge of blade is sharp and other is blunt, C. Round shape wound resulting from round object; D. Fishtail appearance of wound resulting from weapon with one edge sharp and other edge square-off; E. Rectangular shape or slit like wound that is caused due to rectangular objects



Fig. 15.17: Stab wound

Torture Methods

Beating torture

- **Falanga:** Beating on the soles of the feet with canes—also known as falaka or Bastinado
- **Telefana:** Repeated slapping on the sides of the head (ears) by the open palms—may cause rupture of the eardrums
- **Quirofana:** Beating on abdomen

Contd...

Contd...

Electric torture (cattle prod)

- **Piacano:** Placing electric wires in mouth, vagina, anus or over nipples
- **Black slave:** Heated metal skewer inserted inside anus

Near suffocation torture

- **Dry submarine:** Tying a plastic bag over the head upto the point of suffocation
- **Wet submarine (Labaneva/latina/pileta):** Forced immersion of victim's head in water often contaminated with urine or vomitus

Suspension torture

- **Lo Bondero** — By wrist
- **Mercelaga** — By ankles
- **Aeroplane** — Hanging victim upside down and beating on the soles

Forced postures torture

- **Planton** — Prolonged standing
- **Cobellete (saw horse)** — Forced straddling of a bar
- **Parrot's speech (Jock, Paude grava)** — Head down by a horizontal pole placed under the knees with wrists bound to ankles
- **Chepuwo:** Tight clamping of thigh or legs with bamboo

EXTRA EDGE

- **Declaration of Takya:** Guidelines for medical doctors concerning torture and other cruel, inhuman and degrading treatment or punishment in relation to detention or imprisonment. Adopted by the World Medical Assembly, Tokyo, Japan, 1975.

Motor Vehicle Injuries

- **Motorcyclists fracture (Hinge fracture):** Transverse fracture of **base of skull** into anterior and posterior halves.
- **Under running/tailgating:** Motorcyclist may run into the back of a large vehicle (truck) due to its sudden stopping.
- **Aircraft accidents:** MC occur during landing.
- **Whiplash injury:** Acute hyperflexion followed by hyperextension of neck due to violent acceleration or deceleration force applied to front seat passenger.
- **Railway spine:** Concussion of the spinal cord occurs in railway and motorcar collisions.
- **Hyperflexion** is MC mechanism of **fracture of spine**.
- In RTA, if aorta usually ruptures with deceleration, there may be multiple transverse intimal tears adjacent to main tears known as **ladder tear**.

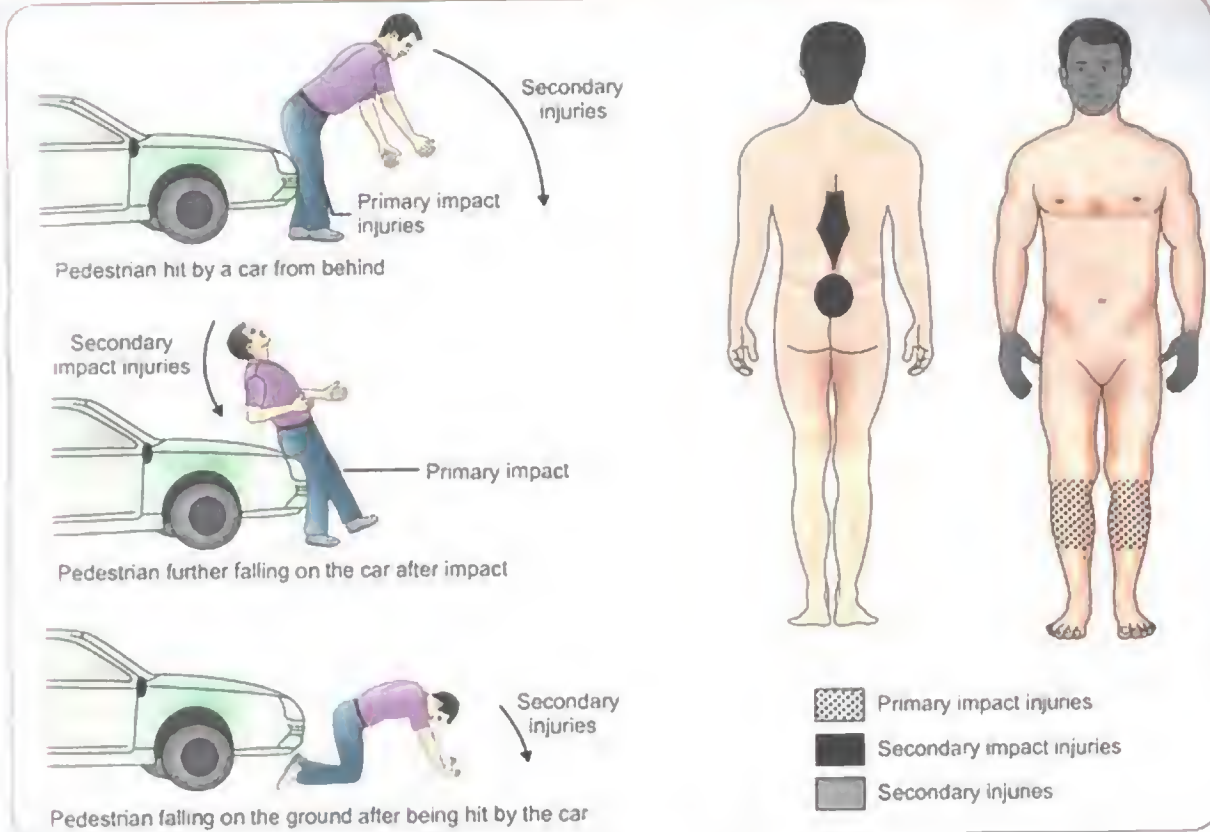


Fig. 15.18: Dynamics of pedestrian injuries and sites of primary impact, secondary impact and secondary injuries

Distinguishing Driver Versus Passenger Injuries

- In motor vehicle accidents it becomes important to differentiate between who was the driver and who was the passenger.
- **Sparrow foot marks** (due to windshield glass shattering - bizarre 'sparrow-foot' shaped lacerations on the face) are seen in BOTH.
- **Steering wheel imprint** is seen only in DRIVER.
- **Seat belt abrasion** is different in both—it is over right shoulder in driver (in Indian cars with right sided steering) and the opposite in the passenger.
- Side window glass causes a characteristic injury since it is made of tempered glass which will shatter into numerous fragments upon impact. These fragments will cause a characteristic 'dicing' pattern of lacerated abrasions on face, shoulders or arms. **Driver will have dicing injuries on the right side of the body** (in Indian cars with right sided steering) and opposite in the passenger.

- **Whiplash injury:** Since the driver anticipates and braces himself for the injury, it is more sudden for the passenger and may be seen more severely in the passenger.

Pedestrian Injuries (Fig. 15.9)

- **Primary impact injuries** indicate that part of the body first struck by the vehicle and often form recognizable patterns (radiator grille; bumper marks etc.); **MC on the legs**.
- **Secondary impact injury**—where the victim is scooped off the ground and thrown onto the vehicle bonnet - head and back may be injured; after this the victim is thrown onto the ground
- **Secondary injuries:** Result from body parts striking the ground — **MC is head injury**.
- **Waddell's triad:** Classic pattern seen in children struck by moving vehicles — **fractured femoral shaft, intrathoracic or intra-abdominal injuries and contralateral head injury**.



Fig. 15.19: Fracture-ala signature

Head Injuries

'Fractures a la signature'	Depressed fractures of the skull since their pattern often resembles the weapon or agent, which caused it
Pond fractures	Occur only in skulls which are elastic , i.e. in infants
Gutter fractures	Due to oblique bullet wounds which remove part of bone
Contre coup fracture	Fracture of the skull occurring opposite to the site of force
Ring fracture	A fracture which runs about 3–5 cm outside the foramen magnum at the back and sides of the skull and passes forwards through the middle and roof of the nose due to which the skull is separated from the spine — occurs due to fall from height and landing on the feet first or head first
Healing	In skull injury healing occurs without the formation of visible callus
Extradural hemorrhage	Usually occurs due to tearing of the middle meningeal artery . Blood is arterial . Lucid interval of few hours to a week is present. It is the least common type of meningeal bleeding
Subdural hemorrhage	Is found in alcoholics and children. Most commonly supratentorial . It is essentially venous or capillary and not arterial
Subarachnoid hemorrhage	MC type of traumatic intracranial hemorrhage
Punch drunk	Traumatic encephalopathy occurs commonly in boxers . Boxers also suffer subdural hemorrhage

GRIEVOUS HURT

Grievous Injury (Section 320, IPC)

- **Emasculation (loss of Potency)**
 - Permanent privation of sight of either **eye**.
 - Permanent privation of hearing of either **ear**.
 - Permanent disfiguration of face (**Vitriolage**).
 - Fracture or dislocation of **Bone or Tooth**.
 - Privation of any **member or joint**.
 - Destruction or **permanent impairing** of the power of any member or joint.
 - Any hurt which endangers life or due to which victim is unable to follow his ordinary pursuits for a **period of 20 days**

Inclusions and Exclusions in Grievous Hurt

- **Emasculation:**
 - This is the **ONLY** clause that applies only to **males**.
 - Emasculation means 'taking away the masculine power, i.e. the power to penetrate during intercourse'
 - It **includes**
 - Cutting off penis (**Bobbitism**)
 - Cutting off artificially constructed penis
 - Trauma to lumbar region (L2-L4, erection NOT possible).
 - It **does NOT** include: **Castration** (cutting off testicles), forced vasectomy, circumcision.
- **Permanent privation of sight of either eye**
 - Privation means **even partial** loss of sight
 - It **includes**:
 - Gouging out the eyes
 - Retinal detachment
 - Hyphema
 - Corneal scar
 - Displacement of IOL.
 - Even though some of these conditions may be operated and vision can be improved—patient's vision may improve following keratoplasty for corneal scar or IOL replacement for displaced IOL etc. BUT it is **still considered a grievous hurt** (operative interference is NOT counted).
 - It **does NOT** include some conditions like **throwing chilli powder** into the eye.
- **Permanent privation of hearing of either ear**
 - Same examples and reasons as above but with respect to the ear.
 - It **includes**:
 - Tympanic membrane rupture (due to slap, etc.)
 - Pouring hot liquid onto the ear
 - Quack inserting stick into ear
 - Displacement of stapedotomy footplate.

Privation of any member or joint

- A '**member**' is any part of the body which is capable of performing a distinct function and/or is **not able to regrow**.

It includes:

- cutting of fingers/hand/feet
- female genital mutilation
- cutting extra finger in polydactyly
- avulsion of nail from base (nail cannot regrow!)
- cutting of a paralyzed/poliomyelitic limb
- cutting of vestigial organ (e.g. appendix)—in cases where not indicated such as a professor of surgery may ask his PG student to remove the appendix for practice/learning in a lapotomy case for some other purpose.

- It **does NOT** include laceration with blood loss; shaving of hair; breakage of artificial limb.

Destruction or permanent impairment of the powers of any member or joint

- This clause is attracted if there is no privation of member or joint (i.e. it is not amputated) but is **rendered functionless**.

It includes:

- striking a hammer on the fingers/hand and reducing it to pulp
- a factory workers hand gets caught in machine and is reduced to pulp.

Permanent disfigurement of head or face

It includes

- Laceration of face (NOT abrasion)
- Branding forehead or cheeks
- Careless suturing of facial wounds
- Cutting off nose and ears
- Injury causing DNS (deviated nasal septum)
- Piercing of nose/ears without consent
- Scar on the face of anyone (unmarried girl, actress or old woman)
- Vitriolage
- Tattooing face without consent

Fracture or dislocation of a bone or tooth

It includes

- Fracture of a bone
- Hairline fracture
- Refracture of partially united fracture (due to a blow)
- Greenstick fracture
- Fracture of sesamoid bone (patella)
- Fracture of hyoid (as in manual strangulation)
- Fracture of outer table of skull (as in gutter fracture)
- Dislocation of shoulder (An example of grievous hurt that can be corrected within minutes!)

- Dislocation of artificial joint
- Dislocation of already loose/damaged tooth
- Dislocation of temporary tooth (a defense that permanent tooth will come in its place is **NOT** acceptable)

- It does NOT include fracture of cartilage.
- A simple cut in the bone is NOT grievous unless it extends upto the **medullary cavity**.

FORENSIC BALLISTICS

Parts of Firearm Weapon

- **Barrel** is a metal tube; **proximal end** is breech end and **distal end** is always open and called **muzzle** end; breech end may have an **extractor** to remove cartridge after firing.
- **Action** — **firing mechanism**; consist of **breech block (bolt)**; firing pin and trigger.
- **Grip** — **butt stock** and
- Magazine

Types of Firearms

- **Smooth bore weapons**: **Shotgun, muskets and muzzle loaders**.
- **Rifled weapons**: Bore is rifled (has longitudinally twisted grooves), e.g. **pistols, rifles, revolvers, sub-machine and machine guns**.
- **Handguns**: **Pistols and revolvers** are smaller handguns.

EXTRA EDGE

- **Calibre (a.k.o Gauge or Bore)**: is **Internal dimension of barrel (bore)** and is given in decimals of inch or mm; It is measured as **distance between 2 diagonally opposite lands of the riflings**.
- **Porodox Guns**: There are some shotguns, which have small portion of their bore near the muzzle end rifled.
- **Air Rifle**: In this compressed air is used to fire lead slugs.

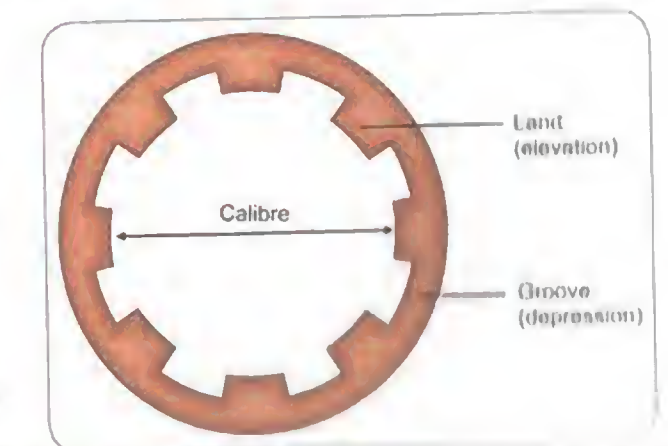


Fig. 15.20: Calibre of rifled firearm (distance between two lands)

Cartridge

- **Cartridge** consists of
 - **Cartridge case** (Cartridge case is *ejected* out automatically in pistols.)
 - **Detonator cap (percussion cap)** is present at the base of the cartridge. **Priming mixture** in *percussion cap* of shotgun cartridge contains **potassium chlorate**.

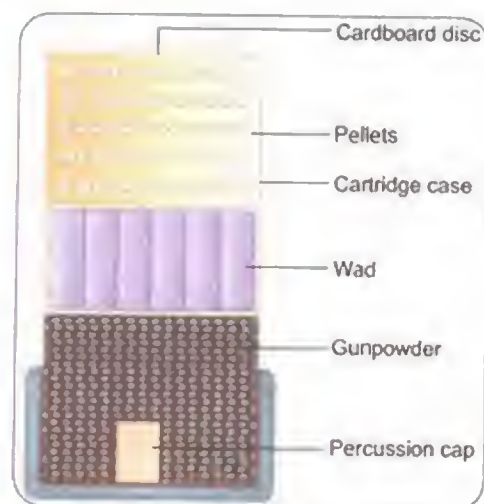


Fig. 15.21: Cartridge of smooth bore firearm

EXTRA EDGE

- **Wads** are present in the cartridge of a **shotgun**; **felt wad** is impregnated with grease and this *lubricates the bore*; allows optimum pressure to develop; seals the bore; prevents the escape of gas from the breech; and separates propellants from the projectiles.
- Constriction of the barrel near the distal/muzzle end of the shotgun is called **choking of shotgun** — **reduces dispersion of pellets**.
- In proximal ballistics, **primer means detonator**.

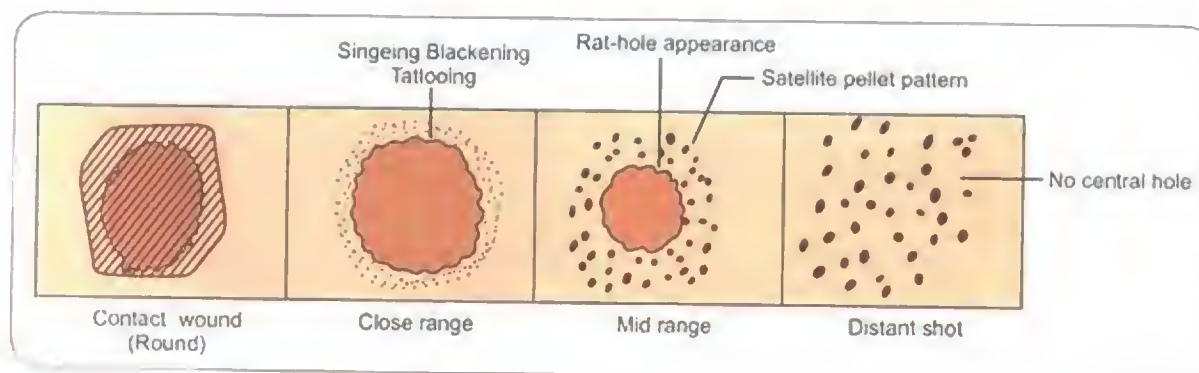


Fig. 15.22: Shotgun wounds at varying distances

Products of a Firing Gun

Product of firing gun	Responsible for	Detected by
Flame	Burning, scorching and singeing	Look at the singed hair around the wound
Smoke	Blackening (smudging)	Wipe the wound with wet sponge; blackening vanishes, sponge becomes dirty
Unburnt powder particles	Tattooing	Wipe the wound with wet sponge; tattooing does NOT vanish; sponge remains clean

Firearms and their Effects Produced at Various Ranges

	Burning and Singeing	Blackening (X 2)	Tattooing (X 3)
Pistols and revolvers	3"→ ↓	6"→ ↓	12-18" ↓
Rifles (X 2)	6"→ ↓	12"→ ↓	24-36" ↓
Shotguns (X 3)	12"→	24"→	48-72"

Mnemonics

- In above table only one number 3 needs to be remembered; rest are multiples as we move across the cells (shown by the arrows). For cms, multiply inches by 2.5.
- Remember the word **TuBBerculoSiS** (for effects from distance to near): Tattooing; Blackening; Burning; Singeing.

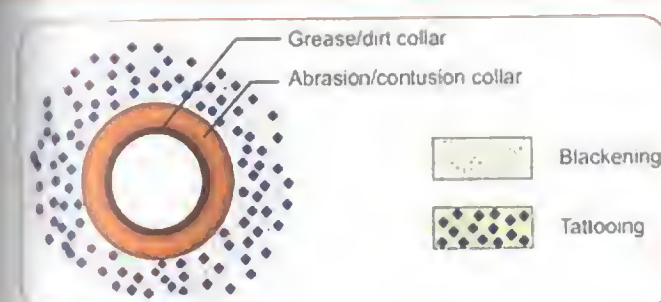


Fig. 15.23: Close shot entry wound of a bullet

From the Above Tables, We Can Infer That

- For **contact** shot: Gases, smoke, unburnt powder enter the wound
- For **near contact** shot: Burning, singeing (flame effects) are present
- For **intermediate** range shot: Tattooing is present; blackening may or may not be present depending on distance
- Very **distant** shot: All are **absent** (NO burning, singeing, blackening or tattooing)
- '**Rat hole**' ('**scalloping**') is a/w **intermediate range** firearm injury of smooth bore firearms.
- **Cherry red color** is seen in **wound track** due to carboxyhemoglobin.

EXTRA EDGE

- In **contact/near contact shot** wound has everted margin and shape is **stellate** or **cruciate**.
- In **contact shot**, due to negative pressure, clothes, hair and blood may enter the muzzle end known as **backspatter**.

Propellant (Gunpowder)

Black gunpowder	Smokeless gunpowder
Consist of potassium nitrate (75%) , sulfur and charcoal	Has in addition to black powder — nitrocellulose, NC (single base) ; or NC + Nitroglycerine, NG (double base) or NC + NG + Nitroguanidine (triple base)

Depending on **fineness**, it is graded as **Fg (Fine grain)**; the more the number of F's the finer are the grains (**FG, FFG, FFFG** etc.).

Produces **MORE** heat, flame and **smoke** Less flame and smoke

Black gunpowder	Smokeless gunpowder
Grains are black	Bright orange to bluish black
One gm produces 3000-4500 cc of gas	One gm produces 12,000-13,000 cc of gas

EXTRA EDGE

- **Pyrodex** is a mixture of black powder and pot. perchlorate, sod. benzoate, dicyandiamide, dextrin wax and graphite

Tests for Gunpowder Residue

- Based on **detection of nitrate**:
 - **Dermal nitrate test** (Paraffin test) using **diphenylamine** reagent — **obsolete** now
- Based on **detection of heavy metal**:
 - **Harrison and Gilroy** test
 - **Neutron activation** analysis
 - **Atomic absorption** spectroscopy.

Types of Projectile (Missile, Bullet)

- **Dum Dum bullet**: **Fragments extensively** upon striking
- **Ricochet bullet**: Bullet hitting on targeted object due to **deflection** after hitting some intervening object
- **Yawning bullet**: Bullet traveling in irregular fashion **instead of nose first** (**causes key hole entry wound**)
- **Tumbling bullet**: Bullet in motion **rotates end to end** (**causes key hole entry wound**)
- **Tandem (piggyback) bullet**: When first bullet fails to leave barrel, on subsequent firing, **2 bullets** are ejected
- **Frangible bullet**: Bullet **designed to fragment into multiple pieces upon impact** and cause more damage
- **Duplex cartridges**: 2 bullets fixed into each other which hit target at different points (separated by as much as 30 cm)
- **Tracer bullet**: Leaves a trace in the atmosphere so that the gunner can observe the strike
- **Souvenir bullet**: Bullet left in the body for long time and is surrounded by fibrous tissue.
- **Incendiary bullets**: contains phosphorus and causes **fire within the target**.

More High Yield About Bullets

- **Tissue damage** (destructive power of bullet) depends more on velocity of bullet.
- **Kinetic energy of bullet** proportional to mass and square of velocity of bullet ($KE = 1/2MV^2$).
- **Comparison microscopes** are used for comparison of bullets.

- The **rotation speed** of a conventional rifle bullet is very high, something in the neighborhood of **3,000 revolutions per second**, depending upon the particular load and cartridge
- On the bullet, **primary markings** (visible to naked eye) help in **identifying manufacturer of gun**, whereas **secondary markings** (seen by microscope) help in **identifying the individual gun**.

Difference between Wounds of Entry and Exit

Trait	Entrance wound	Exit wound
Size	Smaller than diameter of bullet. In close discharge, skin is torn	Bigger than bullet
Edges	Inverted	Everted, puckered or torn
Contusion, abrasion and grease collar	Present	Absent
Burning, blackening and tattooing	May be seen around the wound	Absent
Bleeding	Less	More
Fat	No protrusion	May protrude
Tissues within and around wound	May be cherry red due to carboxyhemoglobin or explosive gases	Absent
Lead ring and metal ring	May be seen around the wound by radiological exam	Absent
Fibers of clothing	Turned In and may be carried into the wound	Turned out

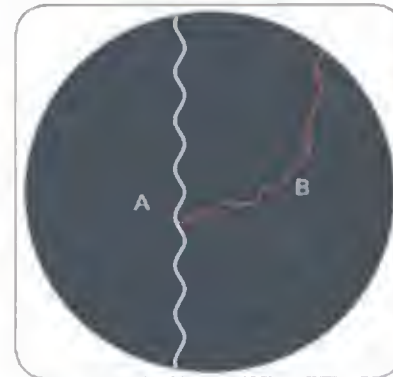
EXTRA EDGE

- In the **skull**, **entry wound** shows bevelling of **inner table** and **exit wound** shows bevelling of **outer table**. (Enter in and Exit out!)
- Doubt as to whether a wound is an **entry wound** or **exit wound** is called **Kennedy phenomenon** (due to surgery/suturing of gunshot wound).

More MCQ Stuff

- **Puppe's rule**
 - Puppe's rule states that when two fracture lines intersect with each other, the **second fracture line never crosses the first one**.
 - It determines the **sequence of shots** when several bullets have struck the cranium and is also applicable to multiple blunt hits to the skull.

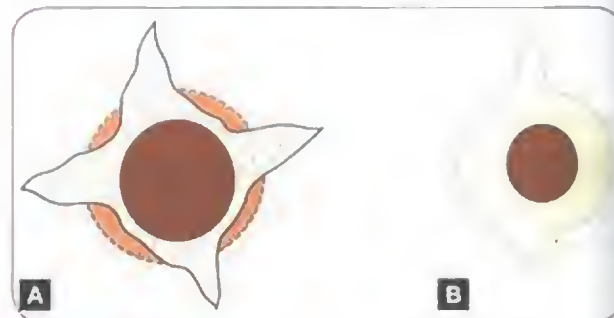
- **Rayalseema phenomenon**: In this phenomenon the person is killed by stab injury and then a **bullet is planted inside the stab injury** to mislead to investigating officer!.



Figs. 15.24A and B: Puppe's rule. A. First (initial) fracture; B. Subsequent (later) fracture

Bomb Blast Injuries

- An explosion or blast produces a **shockwave**. **Air blast (MC)** — cause barotrauma to air filled hollow organs — **tympanic membrane damaged MC**; second MC is lungs.
- **Secondary blast injury** is due to flying debris or missiles; **classical Marshall's triad** is seen — **bruises, abrasions and puncture lacerations**.
- **Molotov cocktail** is an incendiary bomb thrown by hand; bottle filled with petrol and rag to serve as a wick.



Figs. 15.25A and B: Contact wounds. A. Stellate wound; B. Muzzle imprint

INFANTS IN FORENSIC

Pregnancy, Infant Deaths

- **'Fecundation ab extra'**: Pregnancy is possible without penetration of vagina by penis due to deposition of semen on thighs or on vulva.
- **Superfecundation** — It means the **fertilization of 2 ova** that have been discharged from the ovary at the same

period by **2 separate acts of coitus committed at short intervals**. There is a possibility of the twin having two fathers.

- **Superfetation** — It means the **fertilization of a second ovum in a woman who is already pregnant**.
- **Signs of remote delivery in the dead**: Uterus is larger, thicker and heavier; walls are concave from inside forming a wider and rounded cavity. The body of the uterus is twice the length of the cervix. The cervix is irregular in form and shortened, its edges show cicatrices.
- **Braxton Hick's contractions** are **present** even when the fetus is dead.
- **Posthumous child**: A child born after the death of its biological father in a legally married couple. Since the advent of cryopreservation, the semen of the husband can be preserved for a very long time. Widow of a person can desire to be pregnant with the frozen semen of her husband and may give birth to the child — in such cases also the child is called a posthumous child.
- **Suppositious child**: It is a child presented by a woman and the **woman pretends that she has delivered the child**. Actually, the child is not her child, i.e. a suppositious child.
- **Affiliation case (Adoption case)** — A woman may allege a particular man to be the father of her illegitimate child and file a case in the court for fixing the paternity dispute.
- **Disputed paternity** or maternity can be solved by: examination of **blood groups; HLA typing; DNA fingerprinting (most confirmatory)**.
- **Atavism** — The child **does not resemble its parents BUT resembles its grandparents**.
- **Birth in Caul**: Fetus is born with intact surrounding membranes.

Infanticide

- **Infanticide** is unlawful killing of a child under the age of 1 year; punishable under 302 IPC.
- **Feticide** is the destruction of life of the fetus at anytime prior to birth.
- In India the fetus is considered to be viable after **210 days**.
- Deadborn child is one which has died in utero and may show the following signs after delivery
 - **Rigor mortis**
 - **Maceration** — is the process of **aseptic autolysis** and is the usual change when a dead child is in the uterus for 3 to 4 days. Signs of maceration are not seen if the child is born within 24 hrs after death. **Spalding's sign** (skull **bones over-riding each other**) suggest maceration.
 - **Putrefaction**
 - **Mummification**.

EXTRA EDGE

- **Adipocere formation is very rare in dead fetus**.
- It is **impossible to collect blood or to culture tissue from a macerated fetus**; here **placental tissue offers best chance for genetic analysis**.

Test for Signs of Live Birth

- **Static test or Fodere's test**: Weight of lung is 30–40 gm **before respiration** and **after respiration** is 60–70 gm.
- **Plocquet's test**: **Weight of lung** is measured in **relation to body weight** — before respiration = 1/70 and after respiration = 1/35 of body weight.
- **Hydrostatic test or (Raygat's test, first life test)**: Specific gravity of lungs — Before respirations (1.04 to 1.05) and after respiration (0.94)
- **Breslau's second life test or stomach bowel test** — Air is swallowed into the stomach during respiration. If the **stomach and intestine float in water** it is a sign of **live birth**.
- **Wredin's test** — Changes in the middle ear as a sign of live birth is not at all reliable.

Battered Baby Syndrome

- **Child abuse/whiplash shaken baby syndrome or Caffey's syndrome**: Features of a battered baby are:
 - **Bruises of varying age**
 - Burns, lacerations
 - **Retinal and subhyaloid hemorrhages**
 - **Subdural hemotoma**
 - Fracture ribs
 - **Spiral fracture** of long bones, displaced epiphysis
 - **Subperiosteal hematoma**.

FORENSIC PSYCHIATRY

- **Indian Lunacy Act - 1912**
- **Mental Health Act - 1987**, Here, the term 'lunatic' is replaced by 'mentally ill person'.
- Delusions of **jealousy** are seen in chronic **alcoholics**.
- **Oneroid state** — is a **dream like state**, which may last for days or weeks. It occurs in delirium and **early schizophrenia**.
- Mental subnormality is **oligophrenia** or amentia.
- **Intelligence Quotient (IQ)** — Mental age/chronological age × 100.
 - 0 to 20 is **idiot**
 - 20 to 50 is **imbecile**
 - 50 to 75 is **moron**.
- **Testamentary capacity** is the mental ability of a person to make a will.

- **Holograph will** is one which is written by a person in his own handwriting.
- **McNaughten Rule** deals with Criminal Responsibility of the insane (Sec 84 IPC); **McManghten was an accused** who fired the gun BUT was later pronounced insane!
- Insanity produced due to alcohol withdrawal (*delirium tremens*) - NOT criminally responsible; BUT voluntary intoxication is NO excuse and is punishable.
- **Locard's exchange principle** - When any 2 objects come in contact there is always a transfer of material from each object to other.
- **Polygraph (Lie Detector)** is an instrument to detect lies.
- **Polygraph** is an instrument used to detect lies (*lie detector*). The *electrodermal response* in polygraph is called the *galvanic skin reaction* or *GSR*.
- **Narcoanalysis** (truth serum) drugs: used are *scopolamine hydrobromide* and *sodium amytal/sodium pentothal*.
- **Durhan rule and Currens rule**: Accused is not responsible for the act, if his act resulted from mental disease or defect.
- Maximum period of observation for proving insanity is **30 days**.

THERMAL INJURY

Heat and Cold Injuries

- **Neonatal cold Injury** - Symptoms appear in first week of life. Rectal Temperature is usually below 32°C. **Outstanding feature** is swelling and redness of the hands, feet and eyelids. Shivering is **absent**.
- **Heat cramps** = Miner's cramps; Fireman's cramp; Stoker's cramp; A/w **profuse sweating**.
- **Heat Exhaustion** = Heat collapse; heat syncope; heat prostration; scanty sweating.
- **Heatstroke** = Heat hyperpyrexia; sunstroke; systemic hyperthermia; thermic fever; **NO sweating**.
- **Heat prostration** = Heat syncope/collapse; a/w moist, cold clammy skin.
- **Cold effects** = **chilblains; frostbite (congelatio); trench foot/immersion foot**.
- **Frostbite** occurs due to exposure to extreme cold (-2.5°C). Skin becomes **hard and black in 2 weeks**.
- **Paradoxical undressing and hide and die phenomenon** are seen in **hypothermia**.

Electric Injuries

- **Flash burns** - refer to thermal injury due to sudden brief exposure to flame.

- **The Electric mark (aka Joule Burn or Endogenous burn)** is specific and **diagnostic of contact with electricity** and is found at the **point of entry of current**.
- **Crocodile Flush burn** - Multiple burnt or punched out lesions are produced due to **high voltage electric** arc dancing over the body surface over large areas.
- Small balls of molten metal, derived from the metal of the contacting electrode so called **current pearls** may be carried deep into the tissues.
- Skeletal muscle in the path of the muscle may show **Zenker's degeneration**.
- Heat generated by the current may melt the calcium phosphate, which is seen radiologically as typical round density foci. (**Bone Pearls or Wax Drippings**)
- There may be bone necrosis or **zig-zag microfractures**.
- **Lightning Stroke** produces **Arborescent or Fillgree burns (Lichtenberg's flowers)** - **burns are seen as colored branching patterns in inverted tree appearance**.



Fig. 15.26: Arborescent marks in lightning
Courtesy: Dr Shrikant Shinge

Difference between Antemortem and Postmortem Burns

Trait	Antemortem burns	Postmortem burns
Line of redness	Present	Absent
Blister	Contains serous fluid with proteins and chlorides . Base is inflamed	Contains air only. Base is dry, hard and yellow
Vital reaction	Present	Absent
Enzymes	Peripheral zone of burns shows increase in enzyme reaction	Peripheral zone does not show increase in enzyme reaction

Burns

- Presence of carbon particles in the respiratory passages (trachea and terminal bronchioles) on histological examination is **absolute proof of being alive during the fire**, i.e. antemortem burn.
- More than half of deaths from burns occur in **first 48 hours** usually from secondary shock due to extensive **fluid loss from burned surface**.
- **Sepsis** is the most important factor in deaths occurring **4 to 5 days or longer after burning**.
- **Pugilistic attitude** - (**Boxing, fencing or defence attitude**). The characteristic posture of a body which has been exposed to **great heat**; this attitude is due to **coagulation of muscle proteins and dehydration** which cause contraction; occurs in both **antemortem and postmortem burns**.
- **Heat hematoma** is an **extradural hematoma**.
- **Heat fracture** may be seen in **skull**.
- **Carling's ulcers** are sometimes produced in the **gastric antrum and duodenum** after 72 hours in extensive burns of the body.
- NOTE: Cushing's ulcers are a/w head injury, brain trauma; they are deeper and penetrating and may be MC seen in duodenum > stomach.
- Blisters are seen in all forms of burns **except brush burn**!
- In **chemical burn**: **Ulcerated patches** are seen; Hair is **NOT singed**; **blistering is absent** in corrosives (but common with vesicants - mustard gas)
- Blisters are also seen in CO poisoning; deep coma; gasoline exposure; putrefaction; around ligature mark in hanging.

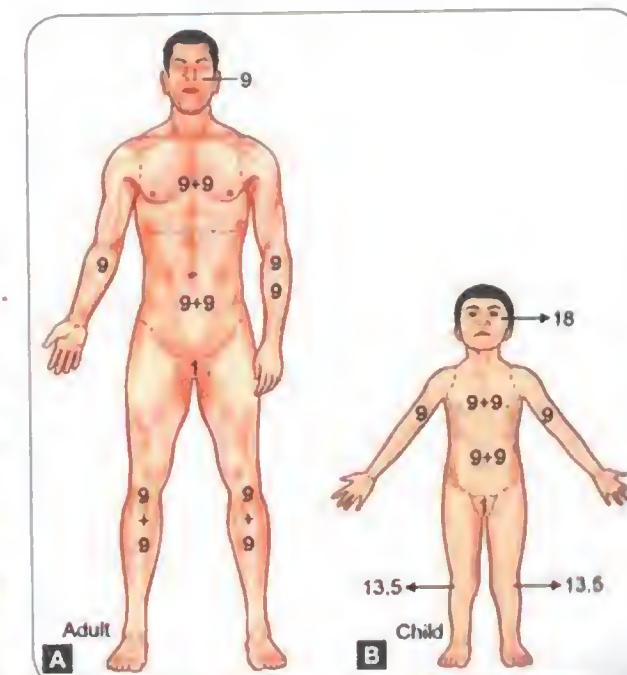


Fig. 15.27: Pugilistic attitude

Classification of Burns

- **Dupuytren's classification**: I - VI degrees of burns
- **Wilson's classification**: I - III degree of burns
- **Modern classification**: superficial and deep burns
- Extent of **burn surface** is calculated by **Rule of nine (Wallace)** for adults; **rule of Lund and Bowder** for children.
- **Genitals** constitute **0% upto 9 years of age** and **head forms the largest area in children**.
- **Area of palm** constitutes about **1% surface area** both in adults and children.

Wallace's rule (Rule of 9)		
Area of body	In adults	In children
Head and neck	9	18
Trunk (front)	18 (front of chest 9 + front of abdomen 9)	18
Trunk (back)	18 (back of chest 9 + back of abdomen 9)	18
Upper limbs	18 (right upper limbs 9 + left upper limb 9)	18
Lower limbs	36 (front and back of right lower limb 18 + front and back of left lower limb 18)	27
Genitals	1	1



Figs 15.28A and B: Percentage of burns in A. Adults; B. Children

Lund and Bowder chart, in children

Area of body (%)	1-4 yrs	5-9 yrs	10-14 yrs
Head and neck	19	15	13
Trunk (front)	16	16	16
Trunk (back)	16	16	16
Upper limbs	19	19	19
Lower limbs	30	34	35
Genitals	0	0	1

RAPE AND SEX-RELATED TOPICS

Virginity

- **Virgin** = woman who has not had sexual intercourse before.
- **Defloration** = loss of virginity
- **Signs of virginity:** *labia majora* are fleshy and elastic; *labia minora* are hidden inside the majora; *clitoris* is small; *vestibule* is narrow; *vagina* is small and tight; *hymen* is intact and inelastic and barely admits tip of little finger.
- **Hymen** is ruptured during the first sexual intercourse (defloration); usually ruptures *posterolaterally*.
- In **children** hymen is *deep seated* and may not rupture during intercourse.
- **Hymen can rupture without sexual intercourse** due to — local injury; gynecological surgery, masturbation, sanitary tampons, salapith.
- Hymen **cannot** rupture by cycling, horseriding, cycling or swimming.
- **Glister Keen rod** is used for *grading of hymenal tear* in a victim of **rape** and to *determine whether rupture is recent or old*.
- **Signs of previous childbirth:** Nulliparous cervix is *conical with a round external os*. In parous women, *cervix is cylindrical and the external os is a transverse patulous slit*.

Rape

Definition of rape

As per **IPC 375**, rape includes sexual intercourse by a man with a woman

- against her will without her consent
- with her consent if she is
 - < 16 yrs of age
 - with his own wife < 15 yrs of age

- Sexual intercourse by a **man with his wife against her will is NOT rape** if she is **> 15 yrs of age** (intercourse with wife below 15 years is considered as rape).

- In India, the law does not presume any limit of age under which a boy is physically incapable of committing rape.
- **Statutory rape:** sexual intercourse with **girl below 18 years with or without her consent**. (Earlier, this was 11 years — amended in the Criminal Law Amendment Act Feb 3, 2013)
- **Date rape:** woman is given a drink with sedative during a **date/party** and raped.

Examination in Case of Rape

- Victim **cannot be examined without written informed consent** in woman > 12 year. If < 12 years signature of parent/guardian is taken (**IPC 90**).
- **Male doctor can examine Female** only in presence of female attendant (**Sec 53(2) CrPC**)
- **Accused can be examined without his consent** 53(A) CrPC.
- **Signs of recent intercourse** — torn frenulum; *vaginal epithelial cells on penis detected by Lugol's iodine*.
- Smegma under prepuce **rules out** recent intercourse.
- **Motile spermatozoa** found on a wet mount of vaginal secretions are indicative of intercourse **within the past 12 hours**. NOTE: Nonmotile sperm may be found in vagina **upto 24 hours** (after this sperm disintegrates).
- **Confirmation of rape by doctor is NOT possible**; only evidence of intercourse can be given and whether RAPE or not will be decided by the court only.
- **Toluidine Blue Dye (TBD)** test 10% dye is used to detect recent microinjuries in genital area; better than colpo scope.

Tests for Seminal Fluid

- **Florence Test:** detects *choline* (Flo-Cho)
- **Barberia's test:** detects *spermine* (Barber-sperm)
- Acid phosphatase test.
- Ammonium molybdate test.
- Creatine phosphokinase.
- Microscopic examination: presence of spermatozoa.
- **Electrophoretic Lactate dehydrogenase isoenzyme detection: absolute proof of semen**
- Ammonium molybdate test
- **UV light:** semen shows blue fluorescence.
- To detect seminal stains on clothes of rape victim, cloth should be examined under - **Ultraviolet light** (shows *bluish white fluorescence*).

Natural Sexual Offences

Rape, Incest (man commits intercourse with blood relation — sister, daughter, etc.); **adultery** (intercourse by man/woman with another person other than spouse). In **India, Incest is NOT a punishable offence**.

Unnatural Sex

- **377 IPC defines unnatural sexual offences.**

Sodomy: Anal sex; buggery (IPC 377)

- If the passive agent is old man/woman = gerontophilia;
- If passive agent is child = pederasty; here the passive agent is called catamite and active agent is pedophile.
- Findings in active agent are fecal soiling, tearing of frenulum, penis shaft is elongated and constricted.
- In habitual passive agent, lateral buttock traction test is positive.
- Tire/Tyre sign: Perianal venous congestion and edema around the anus in anal abuse in children.

- **Tribadism/Leshianism** = Female homosexuality; **active partner is butch or dyke** and **passive agent is femme, NOT an offence** in India.
- **Buccal coltus (slut of Gomorrah): Fellatio** = oral stimulation of penis; **Cunnilingus** = oral stimulation of female genitals; **buccal swabs are useful upto 9 hours**.

Impotence and Sterility

- **Impotence:** Inability to perform sexual intercourse and copulate.
- In **males** impotence is passive leading to **non-erection**; in **females** impotence is active leading to **vaginismus** (spasmodic contraction of vagina due to hyperaesthesia)
- **Infertility:** Failure to conceive (regardless of cause) after **1 year** of unprotected and regular intercourse.
- **Erectile dysfunction**—MC cause is **psychological**.
- **Quod hanc**—A male may be impotent with one particular female but not with others.
- **Frigidity**—inability to maintain sexual arousal pattern in females (absence of sexual desire or inability to achieve orgasm).

SEXUAL PARAPHILIAS

Paraphilias (sexual deviations or sexual perversions or onanisms) refer to preferential use of unusual objects of sexual desire or engagement in unusual sexual activity over a period of at least 6 months, causing **impairment in occupational or social functioning**.

Types of Paraphilias

- **Fetishism:** Sexual preference for inanimate objects (e.g. women's shoes, stockings, bras, rubber sheets).
- **Transvestism or conlsm:** Men gaining sexual gratification from wearing women's clothing, particularly undergarments.
- **Exhibitionism** (IPC 294): Almost exclusively seen in males; Persistent method of sexual arousal by revealing

one's genitals to unsuspecting women so that they will be shocked. This is followed by masturbation to achieve orgasm.

- **Frotteurism:** Obtaining sexual gratification by rubbing the penis against a woman who is nonconsenting and unaware (e.g. in crowded buses).
- **Sadism or masochism:** Obtaining sexual pleasure from giving (sadism) or receiving (masochism) physical pain or humiliation.
- **Voyeurism (scotophilia, peeping tom):** Obtaining sexual pleasure from secretly watching people (often with binoculars) undressing or engaging in sexual activity.
- **Pedophilia:** Obtaining sexual gratification through fantasies or behaviors with children of the opposite or same sex; the pedophile must be at least 16 years of age and 5-year older than the victim.
- **Zoophilia (Bestiality):** Persistent and significant involvement in sexual activity with animals.
- **Telephone scatologia:** Gaining sexual pleasure from making telephone calls to unsuspecting women and engaging them in conversations of a sexual nature.
- **Miscellaneous:** Sexual arousal with urine (urophilia); corpses (necrophilia); feces (coprophilia); enemas (klismaphilia), etc.

Treatment

- Psychotherapy that is psychoanalytically oriented and **aversive conditioning** (e.g. forming an association between mild electric shock and the preferred paraphilia).
- Pharmacologic treatment includes **antiandrogens and female sex hormones** for hypersexuality associated paraphilias.

SUICIDE

- **IPC 309**—Attempt to suicide (no longer valid as an offense).
- **Police Inquest** is done in death by suicide.
- MC method of **suicide in India** is by hanging (41.8%) as per national crime records bureau (2014 statistics).
- **Tentative Cuts/Hesitation marks** seen in **suicidal attempt injury**.
- In 2008, a series of suicides planned over the Internet in Japan came to be known as **The Japanese Detergent Suicide technique** which involves mixing toilet cleaner and bath salts to create **hydrogen sulfide gas (rotten eggs odor)**.
- **Parasuicide** ('near suicide') is a **suicide attempt; a non-fatal act (no result in death)** in which a person **deliberately causes injury to him or herself or ingests**

any therapeutic dose in excess; **MC method for parausuleide is self poisoning with drugs.**

- **Harakiri** most often refers to a form of **seppuku** (or ritual suicide) in Japan — stomach-cutting; 'abdomen-cutting' with a short blade; was used by the Samurai.

HISTORY OF FORENSIC MEDICINE

- **Code of Hammurabi** is the oldest known medicolegal code.
- **Chinese medicine** is probably the **world's first organized body of medical knowledge** that dates back to 2700 BC.
- **Manu** was the first traditional king and lawgiver in India; Manusmriti talks about rules for marriage, punishment for adultery, incest and sexual offences.
- In ancient history, the first medicolegal autopsy was performed by Roman physician **Autistius on the body of Julius Caesar** after his assassination.
- In modern history, the **first medicolegal autopsy** was performed by **Bartolomeo da Varignana** of BOLOGNA, Italy.
- In **India**, the **first recorded medicolegal autopsy** was performed by **Dr Edward Bulkley** in **Cheennai**.
- First book of forensic medicine - **Fortunato Fedele**.
- The greatest of all works of forensic medicine was '**Questiones Medicolegalis**' — by Paulus Zacchias

TESTS FOR BLOOD

Nature of stain (Is it blood or not?)

Chemical tests

These tests are based on **peroxidase** activity of **hemotin** which is derived from the oxidation of hemoglobin or methemoglobin. **Peroxidase in the presence of H_2O_2** converts colorless salts into colored bases.

- **Benzidine Test:** (Glacial acetic acid + H_2O_2); gives **greenish blue color**; **Best preliminary test**.
- **Phenolphthalein test (Kastle Meyer test):** Deep permanganate test
- **Leucomalachite green test:** Peacock green color
- **Gualacum test:** Blue color
- **Orthotolidine test (Kohn test):** Blue green color
- **Amidopyrine test:** Purple color

Microchemical tests

- These tests are based on the property of heme part of hemoglobin to form colored crystals.
- **Teichmann's Hemin crystal test.**
- **Takoyama's Hemachromogen crystal test:** test, gives good result even with old stain
- **Luminal spray test:** Specially useful for **old obscure** blood stains.

Contd...

Spectroscopy

- **Most delicate and reliable test** (even with < 0.1 mg blood), **positive with fresh and old stains**

Detection of species (human or animal blood?)

- **Precipitin test** is used to test whether blood-stains are human or not.

Detection of blood group of blood stain

- **Latte's crust** method
- **Enzymological** methods: vertical disc; vertical or horizontal slab; isoelectric focusing; cellulose acetate membrane).
- **Immunoagical** (serologic): Absorption elution test; (**Acid dilution** or Acid elution test); absorption-inhibition test; mixed agglutination test; latex test.

STARVATION DEATHS

- In **starvation**, there is **shrinking of all internal organs except brain**.
- **Starvation** is a/w **distended gallbladder** (due to accumulation of bile from lack of stimulation by food).
- **Feeling of hunger with hunger pain** lasts for **36-48 hours** of starvation.
- **Adult** may survive without food and water (death may occur in) for **10-12 days**.
- **Last to disappear is the buccal fat** (Bichat fat pad) in starvation.
- **Brain** in starvation uses **ketone bodies**.

MISCELLANEOUS HIGH YIELD

- **Gold chloride** is used in **corneal tattooing**.
- **Duret hemorrhages:** seen in the **medulla or pons** of patients who are **rapidly herniating**.
- **Karyotyping** of human chromosome may be done with **lymphocytes; bone marrow; fibroblast, skin, amniocytes and chorionic villus**; but **NOT** monocytes.
- **Leudrum staining (phloxine tartrazine)** is used in **amniotic fluid embolism** to detect squames.
- **Lyonization or X chromosome inactivation** occurs about the **16th day** of life. One of the 2 X chromosomes in female cells is inactivated and appears as a dark staining mass (**Barr body; Davidson body**) in the nucleus of up to 6% of cells.
- **Judicial electrocution** (electric chair) is carried out in some states of **USA**.
- **Postmortem clot** is characterized by **chicken fat** clot.
- **Potassium dichromate** oxidation of alcohol to acetic acid is the basis of **alcohol breath tests** used by the police in **breathalyzers**.

Contd...

- A person attains **majority on completion of 18 years**. However if the person is under the **guardianship of the court, he attains majority after 21 years** (Indian majority act).
- The relationship **between trauma and neoplasia** is given by **Ewing's postulates** which must be fulfilled before trauma may have been legally said to have caused malignant disease (**He is the same Ewing from Ewing's sarcoma!**).
- Deaths and births should be registered **within 21 days**.
- **Barbiturate** blisters: It is also known as coma blisters, friction blisters, barb burns seen in barbiturate poisoning.
- **Dangerous wound:** It has not been defined in the IPC. Dangerous wounds are those which cause imminent danger to life by its direct or imminent effects because of its being extensive in nature, involving important organs of the body and also likely to prove fatal in absence of medical/surgical aid. Examples: tear in dura mater; laceration of lung (resulting in hemothorax), cerebral edema, perforation of GIT, rupture of large arteries/veins.
- **Istanbul protocol:** 'Manual on Effective Investigation and Documentation of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment', commonly known as the Istanbul Protocol, is an official United Nations document. The Istanbul Protocol is intended to serve as a set of international guidelines for the assessment of persons who allege torture and ill treatment, for investigating cases of alleged torture, and for reporting such findings to the judiciary and any other investigative body.

DECLARATIONS OF WORLD MEDICAL ASSOCIATION

WMA location	Declaration
Declaration of Geneva (1948)	Modernised version of Hippocratic Oath
Declaration of London (1949)	International code of medical ethics
Declaration of Helsinki (1964)	Human experimentation and clinical trials
Declaration of Sydney (1968)	Definition of Death
Declaration of Oslo (1970)	Therapeutic (legalised) abortion
Declaration of Munich (1973)	Discrimination in medicine
Declaration of Lisbon (1981)	Rights of patients
Declaration of Venice (1983)	Terminal illness
Declaration of Malta (1992)	Role of doctor in hunger strikes

WMA location	Declaration
Declaration of Tokyo	Guidelines for doctors in cases of torture

Surrogacy (Regulation) Bill, 2016.

- The Bill defines **surrogacy** as a practice where a woman gives birth to a child for an eligible couple and agrees to hand over the child after the birth to them. The Bill allows **altruistic surrogacy** which involves a surrogacy arrangement where the monetary reward **only** involves medical expenses and insurance coverage for the surrogate mother.
- **Commercial surrogacy** (being a surrogate mother for exchange of money) is **prohibited** under the Bill.
- Note: **Altruistic surrogacy** - where surrogate mothers undertake surrogacy on grounds of **love and compassion** without expecting any monetary benefit in return.
- The Bill states that any child born out of a surrogacy procedure shall be the **biological child of the intending couple** and will be entitled to all rights and privileges that are available to a natural child

Conditions to be fulfilled/ proved by the couple intending to commission the surrogacy	Conditions to be fulfilled/proved by the surrogate mother
--	---

- | | |
|---|--|
| <ul style="list-style-type: none"> • The couple must be a close relative of the surrogate mother. (BUT the bill does NOT define the term 'close relative') • They are Indian citizens who have been married for at least 5 years. • They are in the age group of 23-50 years (female partner) and 26-55 years (male partner). • A medical certificate stating that either or both partners are infertile. • They do not have any surviving child (whether biological, adopted or surrogate), except if the surviving child is mentally or physically challenged or suffers from a fatal illness. • A court order concerning the parentage and custody of the child to be born through surrogacy. • Insurance coverage for the surrogate mother. | <ul style="list-style-type: none"> • She has to prove that she is a close relative of the couple intending the surrogacy • She was or is married and HAS a child of her own • She is 25 to 35 years old. • She has not been a surrogate mother before. • She possesses a medical certificate of her fitness for surrogacy. • She can act as a surrogate ONLY ONCE in her lifetime. |
|---|--|

Toxicology

Exceptions

- *Single parents, homosexuals, live-in couples, foreigners cannot ask for surrogacy.*
- *Childless or unmarried women are not allowed to be surrogate mothers.*

Penalty

- The Bill specifies that any person who takes the aid of a doctor or a surrogacy clinic in order to conduct

commercial surrogacy will be punishable with imprisonment for a minimum term of *five years and a fine that may extend to five lakh rupees.*

- Offences such as (i) undertaking or advertising commercial surrogacy; (ii) exploiting or abandoning the surrogate mother or child; and (iii) selling or importing human embryo or gametes for surrogacy will attract a minimum penalty of *10 years and a fine up to 10 lakh rupees.*

GENERAL TOXICOLOGY

History of Toxicology

- *Paracelsus* is the *father of toxicology.*
- *Mathieu Orfila* is considered the *father of modern forensic toxicology.*
- *Drugs and Cosmetics Act, 1940:* Aims to control quality, purity and strength of the drug; amended in 1961 to include Ayurvedic and Unani medicines, the label of medicines should display the ingredients of the drug.
- *Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985* provided for identification, treatment and rehabilitation of drug addicts.

Classification of Poisons

- *Deliriant poisons:* *Datura atropa*, *belladonna* and *cannabis.*
- *Cardiac poisons:* *Aconite*, *oleander*, *nicotine* and *digitalis.*
- *Spinal poisons:* *Strychnine (nux vomica)* and *gelsemium.*
- *CNS depressants:* *Opioids*, *alcohol*, *anesthetics* and *hypnotics.*
- *Corrosive poisons:* *Sulfuric acid*, *nitric acid*, *hydrochloric acid*, *oxalic acid* and *carbolic acid.*

Other Important Points in Treatment

- *Forced alkaline diuresis* is used for *barbiturates (phenobarbitone)* and *salicylate poisonings.*
- *Acid diuresis* is used for *amphetamines*, *cocaine* and *phenacyclidine (NOT used now).*
- *Saline diuresis* is useful for *alcohol*, *thallium*, *bromide*, *lithium* and *isoniazid.*
- *Hemodialysis* is NOT useful in *copper sulfate*, *benzodiazepines*, *organophosphates*, *kerosene* and *digitalis poisoning.*
- The *Universal Antidote* is a mixture that contains *activated charcoal*, *magnesium oxide* and *tannic acid; the mixture is ineffective and no longer used.*

Odors in Poisonings

Odors	Poisonings
Bitter almonds	Cyanide (HCN), prussic acid
Garlicky	Arsenic , Zn-P < Al-P (celphos), Phosphorus, malathion, parathion
Rotten Egg	Hydrogen Sulfide (H2S), mercaptans, disulfiram
Burnt rope	Cannabis
Fruity	Ethanol, chloroform, acetone
Fishy or musty	Zinc phosphide
Acrid (pear like)	Chloral hydrate, paraldehyde
Phenolic, disinfectant like	Carbolic acid
Shoe polish like smell	Nitrobenzene
Coal gas like smell	Carbon monoxide

Diseases Resembling Natural Diseases

Poisons	Disease
Arsenic	Cholera Fading measles Addison's disease
Strychnine	Tetanus
Zinc	Malarial Chills
Thallium	Natural death Guillain-Barre syndrome Porphyria
Di-nitro compounds	Thyrotoxicosis
Organophosphates	Bronchial Asthma

Urine Discoloration

Urine color	Poison/drug
Orange	Rifampicin
Green	Carbolic acid
Purples	Porphyrias, Phenolphthalein
Red or pink	Aminopyrine, Aniline, Desferrioxamine
Reddish brown	Chloroquine, Ibuprofen, Iron, Phenacetin, Phenytoin, Phenothiazines, Metronidazole, Methemoglobin
Brownish black	Phenol, Cresol, Naphthol, homogentisic acid

Contd..

Urine color	Poison/drug
Yellowish brown	Furazolidone, Nitrofurantoin, Sulfamethoxazole
Yellow	Fluorescein dye, Riboflavin, Quinacrine
Yellowish orange	Warfarin, Carrots, Vitamin A
Greenish blue	Chlorophyll, Breath Mints, Methylene Blue, Thymol
Brownish green	Methocarbamol, Resorcinol

Poisons causing miosis (constricted pupils)	Poisons causing dilated pupils (mydriasis)
<ul style="list-style-type: none">OrganophosphatesOpioids (morphine)BarbituratesMushroomEarly nicotine poisoningPontine hemorrhageCholinergic drugs	<ul style="list-style-type: none">Datura (atropine or belladonna)Anticholinergic drugsAnoxiaCyanide

EXTRA EDGE

Hippus (alternate constriction and dilation) seen in **aconite and borbiturate** poisonings.

Appearance of Stomach in Poisonings

Poison	Appearance
Sulfuric acid	Soft
Alkali	Bleached, sodden
Phenol	Leather like
Oxalic acid	Scalded

Other Unique Poisoning

- **Poisons causing early appearance of rigor mortis:** Strychnine, hydrocyanic acid
- **Poisons causing perforation of stomach:** Sulfuric acid and hydrochloric acid
- **Poisons causing cerebral edema:** Alcohol, organophosphate, aluminium phosphide
- **Poisons resisting decomposition/putrefaction:** Carbolic acid, arsenic, datura, alcohol

Chelation Agents for Heavy Metal Poisons

Antidote	Indication
Desferrioxamine	Iron
Prussian blue	Thallium
Sodium calcium edetate (EDTA)	Heavy metals (esp. lead)
Succimer (DMSA, dimercapto-succinic acid)	Heavy metals (esp. lead and arsenic)
Penicillamine	Copper

Special Viscera Preserved

Heart	Cardiac poison (digitalis)
Spleen	Cyanide poisoning (best organ)
Bone (shaft of femur); Hair and Nails	Heavy metals Thallium, Antimony, Arsenic and Radium
CSF	Alcohol (fluoride is preservative)
Vitreous	Alcohol, chloroform (fluoride is preservative)
Lung	Gaseous poisons like CO, cyanide, chloroform

- **Viscera to be preserved in suspected case of poisoning are:** Stomach and its contents; Upper part of small intestine (30 cm in adults; BUT full in infants); Liver about 500 gm (BUT full liver in infants); one kidney or half of each kidney; blood (10–20 mL); urine (30–50 mL)
- Preservative used is **saturated sodium chloride solution** (common salt)—**EXCEPT in vegetable poisoning** (including aconite) and inorganic mineral acid (**corrosives**) poisoning.
- **Rectified spirit** can also be used to preserve viscera in all **EXCEPT PAPP** (Phosphorus, Alcohol; Phenol; Paraldehyde, Acetic acid) poisonings.
- The viscera should **NOT** be preserved in formaldehyde.
- For **suspected rabies brain** should be preserved in **50% glycerol**.
- **Spinal cord** is preserved in **strychnine and gelsemium** poisoning.
- **Blood or splenic tissue** is the best specimen for DNA analysis.



Fig. 16.1: Ewald tube used for gastric lavage

Drugs and Their Antidotes

Drug	Antidote
Paracetamol; Aspirin	N-Acetylcysteine or methionine
Anticholinergics (e.g. atropine/Belladonna)	Physostigmine
Anticholinesterases (organophosphates)	Pralidoxime (cholinesterase reactivator) and atropine (competitive antagonist at acetylcholine receptor)
Benzodiazepines	Flumazenil
Carbon monoxide	Oxygen
Digoxin	Sodium thiosulfate, sodium nitrite
Heavy metals (Arsenic, mercury or gold)	Fab antibody fragments to digoxin
Heparin	Dimercaprol or D-penicillamine
Isotiazid	Protamine sulfate
Iron	Pyridoxine
Lead	Desferrioxamine (chelating agent)
Lead	Penicillamine or calcium sodium edetate
Methanol	IV ethanol (competes with alcohol dehydrogenase)
Opiates	Naloxone/Naltrexone (competitive antagonist at opiate receptor)
Warfarin	Vitamin K

CYANIDE POISONING

- **Hydrocyanic acid = HCN, Prussic acid or Scheele's acid.**
- HCN is a **vegetable acid** in leaves and fruits of almonds, cherry, pear, plum etc. in form of **amygdalin**.
- **Lauusin** converts this to cyanide in presence of **bacteria of small intestine**.
- **Young linseed plant** yields **free HCN**.
- **Prolonged nitroprusside infusions** can cause cyanide toxicity.
- Cyanide **inhibits cellular respiration** (causes cellular asphyxia) by **inhibiting the action of cytochrome oxidase—death is due to histotoxic (cytotoxic) hypoxia**.
- **Potassium ferrocyanide is a nonpoisonous salt of cyanide.**

Postmortem Changes

- Externally: **Fixed dilated pupils; odor of 'Bitter Almonds'** is noted in breath and vomit; Postmortem hypostasis is **classically cherry red** (sometimes options given as **bright red or pink** in exams!).
- Internally: Mucus membrane of stomach is congested and red; since its **corrosive erosions** and **hemorrhages in walls of stomach** and **frank blood in its lumen** may be seen.

- **Achlorhydric patient** do **NOT** suffer from **cyanide poisoning** as conversion into chlorides and hydrocyanic acid by HCl does not occurs.
- **Lee Jones test** is used for **cyanide poisoning**.
- **Fatal blood cyanide level** is **> 3 microgram/mL**; as **hydrocyanic acid** it is **50–100 mg**; as **potassium cyanide** it is **200 mg**.
- To treat cyanide poisoning: **Amyl Nitrite** (Inhalation—to convert hemoglobin to methemoglobin), **Sodium Nitrite**, **Sodium Thiosulfate**, **Methylene blue**, **PAPP** (Para-Aminopropiophenone) may be used.
- **Lilly's cyanide antidote kit** = (amyl nitrate + sodium thiosulfate + sodium nitrite).

OXALIC ACID POISONING

- Also known as '**salt of sorrel**' or '**acid of sugar**'; occurs in **leaves of rhubarb**.
- **Oxalic acid** used for **erasing writing and signature illegally**.
- Can cause **hypocalcemia** and **tetany**; **shock** and **oxaluria**; it is **corrosive**—can cause **coffee grounds vomitus**.
- **Antidote for oxalic acid poisoning** = **Calcium lactate or gluconate**.

Carbolic acid (Phenol) poisoning

- Pure carbolic acid has **needle like crystals**; poisoning is called **corbolism**; has **phenolic smell**.
- It is **corrosive poison**; **corrosion of lips/mouth/tongue** may occur; vomiting may **NOT** take place due to **anesthetic action on stomach**; **Stomach** looks **brownish and leathery**; **Pupils are constricted**.
- Urine in **Phenol** poisoning is = **Olive Green** or even black on exposure to air = **corbolorio** is due to oxidation of phenol to **hydroquinone** and **pyrocatechol** (these may cause **ochronosis - pigmentation in various cartilages and corneo**); **proximal tubular necrosis** occurs.
- Chronic carbolic acid poisoning is also called **phenol morasmus**.
- **Ferric chloride test:** Urine turns blue on adding this to urine of phenol poisoned patient.

SULFURIC ACID POISONING

- Sulfuric acid is = **Oil of vitriol**
- **Vitriolage** = **Throwing of sulfuric acid** on another person—classified as **grievous injury (sec 320 IPC)** and causing **disfigurement (sec 326 IPC)**.
- A **very strong corrosive**.
- **Stomach** is a soft, spongy brown black mass which **disintegrates when touched (blotting paper stomach)**—highest chances of stomach perforation among any acid
- **Fatal period** is **12–24 hours**.

MORE HIGH YIELD CORROSIVE POISON POINTS

- All mineral/inorganic acids cause = **Coagulation necrosis except hydrofluoric acid** which causes **liquefaction necrosis**.
- Nitric acid causes **yellow discoloration of GIT and tissues** = Due to production of **picric acid (Xanthoproteic reaction)**.
- The only absolute CI for gastric lavage is **corrosive poisoning (EXCEPT carbolic acid)** due to **danger of perforation**. It is relatively contraindicated in **kerosene poisoning** due to risk of **aspiration pneumonitis**.
- **Stomach mucosal folds are brownish in hydrochloric acid poisoning**.

PHOSPHORUS POISONING

- Phosphorus is a **protoplasmic poison**, which affects cellular oxidation; causes **anoxic necrobiosis** affecting **liver; used in fireworks (diwali poisoning)**.
- **White phosphorus** is found in **fertilizers, rodenticides (rat poison)**; It is **translucent, waxy and luminous (phosphorescence—so vomit and feces glow in the dark!—smoky stool syndrome)**; **Breath and excreta have garlicky odor in white phosphorus poisoning**; (remember that garlic is white in color).
- **Red phosphorus** on sides of **match box** (and Red = fire); but **nontoxic**.
- **Phossy jaw**: In chronic phosphorus poisoning **necrosis of the lower jaw** in the region of a decayed tooth occurs.
- White phosphorus oxidises and emits **white fumes, ignites at 34°C under water**.
- **Copper sulfate** is used to precipitate phosphorus.
- To preserve luminosity; **viscera are preserved in saturated saline solution**.

ARSENIC POISONING

- Metallic arsenic is **NOT** poisonous, as it is **NOT** absorbed from the alimentary canal.
- **Arsenic or white arsenic is arsenious oxide or arsenic trioxide (Sankhya or Somalkhar)** is the MC form of arsenic used.
- Copper arsenite is **Scheele's green**; Copper acetoarsenite is **Paris green**.
- Arsenic combines with **sulphydryl enzymes** and **interferes with cell metabolism**.
- Most popular **homicidal poison**.
- **Fatal dose of arsenic is 100-200 mg (0.1-0.2 g)**.

Acute Poisoning

- Resembles **cholera**, gastroenteritis type; **garlicky odor**. X-ray abdomen may reveal ingested arsenic, which is **radioopaque**.
- Arsenic is rapidly cleared from blood and distributed to various organs (**liver > kidney > spleen**). Blood sample is useful only in acute poisoning. Arsenic does NOT cross blood brain barrier and hence **least amounts found in brain**.

Chronic Poisoning

- Skin and nail changes, such as **hyperkeratosis of palms and soles**, 'rain drop' **hyperpigmentation**, exfoliative dermatitis, and **Mee's lines** (transverse white striae of the fingernails).
- **Sensory and motor (mixed) polyneuritis** manifesting as **painful paresthesias of hands and feet** in a 'stocking-glove' distribution.
- **Subendocardial hemorrhages** of the left ventricle.
- **Stomach mainly affected** and shows **red-velvety appearance**.
- Chronic consumption of water containing arsenic at high concentrations leads to vasospasm and peripheral vascular insufficiency culminating in 'blackfoot disease', a gangrenous condition affecting the extremities.
- Risk of **skin cancer** and possibly of **cancers** of the lung, liver (**angiosarcoma**), bladder, kidney, and colon.



Fig. 16.2: Arsenic poisoning—Hyperkeratosis



Fig. 16.3: Raindrop pigmentation—arsenic poisoning

Tests

- **Marsh test and Reinsch tests** are positive.
- Arsenic can be detected in completely decomposed bodies since it is present in **hair, nails and bones**.
- **Arsenic delays rigor mortis and retards putrefaction**.

Treatment

- **Freshly prepared hydrated ferric oxide (Fe_2O_3)** is **arsenic antidote**; Dialysed iron may be used as substitute.
- Alkalis should NOT be given as they increase the solubility of arsenic.



Fig. 16.4: Mee's lines

MERCURY POISONING

- Mercury is also called **quicksilver**.
- **Mercuric chloride** is **most poisonous salt** of mercury.
- **Acute poisoning—nephropathy (proximal tubular)**; **grayish white mouth and tongue**.

Chronic Poisoning

- **Excess salivation**; **Blue line** at junction of teeth with gums.

- Anorexia, insomnia
- **Fine tremors** of the hands (first), tongue, arms and later of legs in mercury poisoning are called **Hatter's shakes** (seen in Hat makers; also was seen hat makers in Danbury, USA—so **Danbury tremors**) or **glass blower's shakes**.
- **Mercurial Erethism** is seen in persons in mirror manufacturing firms and is characterized by **shyness, timidity, irritability and insomnia**.
- **Mercurialentitis** is due to **rust-brownish deposit of mercury on the anterior lens capsule**; it is bilateral and has no effect on visual acuity; it is due to exposure to the vapor of mercury.
- **Acrodynia** or **Pink disease**: exposure of **children** to mercury in any of its forms can this **generalized body rash**.
- Characteristic changes involve ascending and transverse colon; resemble '**Diphtheric colitis**' or '**bacillary dysentery**'.
- **Minamata disease**—Organic mercurial poisoning due to eating of **fish poisoned by mercury**.
- Mercurous chloride is known as **calomel**.
- Maternal intake of organic mercurial compounds during pregnancy may lead to **cerebral palsy in neonate**.
- **Antidote of choice** for mercury poisoning—**BAL (British Anti Lewisite - dimercaprol)**; Ca-EDTA should NOT be used as it increases nephrotoxicity.
- Albumin precipitates mercuric chloride.



Fig. 16.5: Acrodynia or 'pink disease'

LEAD POISONING

- Lead is **poisonous in its native form**; main salts causing toxic effects are **lead acetate, lead carbonate, lead monoxide, lead sulfide (least toxic)**.

- Sources: *Lead paints*, water contaminated by *lead pipes*, use of *kohl cosmetics*.
- *Facial pallor* particularly around the mouth is the most consistent sign.
- *Microcytic hypochromic anemia*, *basophilic stippling*—early sign.
- *Colicky abdominal pain and constipation*—later sign.
- Encephalopathy, motor neuropathy, headache.
- Nephrotoxicity, hypertension, hypocalcemia.
- **Burtonian line**: *Stippled blue line on the gums*, esp. *upper jaw* (due to *lead sulfide*).
- With prolonged exposure to lead, normal excretion of uric acid is impaired causing *saturnine gout*.
- Chronic *lead poisoning* is *plumbism* or *saturnism*.
- *Lead palsy*—*peripheral neuropathy* causing *wrist and foot drop*.
- Nephropathy—proximal tubular necrosis.

Investigations

- *Peripheral smear* and blood counts, abdominal X-ray for children to *detect Pica*.
- Long bone X-ray for children for '*lead lines*' at *metaphysis* of long bones.
- Presence of $\frac{1}{4}$ mg of lead per liter in urine is diagnostic; Increased *coproporphyrin urine* (CPU) levels *0.25 mg/l of lead* is diagnostic.
- *Zinc protoporphyrin* and *free erythrocyte protoporphyrin* levels *above 50 mg/100 ml* indicate poisoning.
- *Bone marrow* shows hyperplasia of leucoblasts and erythroblasts with a decrease in fat cells.

Treatment

Chelation therapy with *sodium calcium edetate (EDTA)*.



Fig. 16.6: Increased metaphyseal density—lead poisoning



Fig. 16.7: Burtonian line

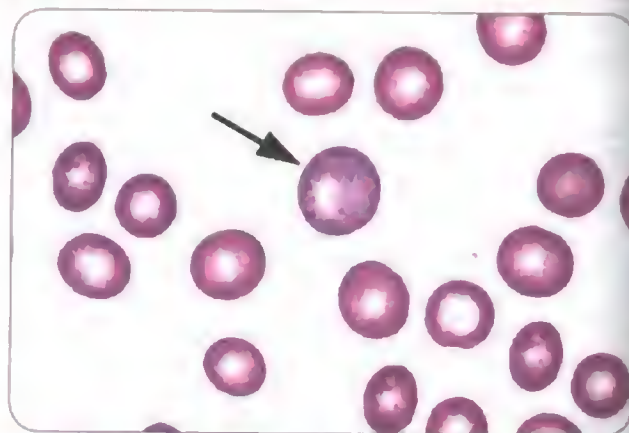


Fig. 16.8: Basophilic stippling

COPPER POISONING

- *Copper sulfate (blue vitriol)* and *copper subacetate* are poisonous; fatal period with copper salts in 1-3 days; *acute hemolysis*, *blue green vomiting*; *diarrhea*; *renal failure*, *purple line along gums* (*Corrigan's sign*), *ptyalism* (excess salivation).
- *Copper sulfate* used to prevent mildew in grape vineyards has given rise to a granulomatous disorder called *vineyard sprayer's lung*.
- *Penicillamine* chelates copper.

OTHER METALLIC IRRITANTS

- *Zinc*—*metal fume fever*—a self limiting influenza like syndrome (*flu like illness*); temperature returns to normal with sweating and chills, mimicking malaria, only *paracetamol* required for treatment.
- *Cadmium* causes *Itai-Itai disease*; *bone pain* and *proximal tubular necrosis*.

- *Blue line on gums* classically seen in *lead poisoning*—may also be seen in *mercury*; *copper*; *bismuth*; *iron poisoning*.
- *Triad of gastroenteritis, hair loss and polyneuritis* is an indicator of *thallium poisoning*.

ALUMINIUM PHOSPHIDE (CELPHOS)

- Used as insecticide and pesticide; on contact with moisture it liberate *phosphine*.
- Phosphine acts by *inhibiting electron transport system* mainly *cytochrome oxidase*.
- Clinically—*garlic odor*; *myocardial necrosis*; *metabolic acidosis*; *esophageal strictures and fistula*; *cardiogenic shock*.
- Gastric lavage gives *black color on presence of silver nitrate* and blue color with ammonium molybdate.

Organophosphate poisoning

- *Organophosphates* are *irreversible anticholinesterases*—by phosphorylating catalytic site of the enzyme.
- Insecticides: *Dyflor (DFP)*, *echothiophate*; *parathion*, *malathion*, *diazinon* - *TIK 20* (all).
- Nerve gases for *chemical warfare*: *tabun*, *sarin*, *soman*.
- Symptoms: *Kerosene like odor*; *increased secretions* (*Diarrhea, Urination, Lacrimation, Sweating, Salivation*); *Miosis*, *Bronchospasm*, *Bradycardia*, *Excitation of skeletal muscle* (*fasciculation, tremor*), *pulmonary edema*; *chromoacryrrhea* (*red color tears*—due to abnormal porphyrin metabolism).
- *Intermediate syndrome*—4 days after ingestion—*muscle weakness, cranial motor nerve palsies and respiratory paralysis* may occur.
- Diagnosis confirmed by estimating *RBC cholinesterase levels*.
- Treatment: *Atropine IV* (*muscarinic antagonist, does NOT reverse muscular paralysis*) and *cholinesterase reactivators* (*Pralidoxime, 2-PAM*) is a *specific antidote* that reverses organophosphate binding to the cholinesterase enzyme—only effective if given *within 24 hours* (otherwise 'aging' occurs). When cyanosis is present, maximum oxygenation should be given before giving atropine to *avoid increased risk of ventricular tachycardia*.

OTHER AGRICULTURAL POISONS

- *Carbamates* are *reversible anticholinesterases*; (*Physostigmine, neostigmine, pyridostigmine, ambenonium, edrophonium, demecarium*); cause *reversible carbamylation*; *Atropine* is specific antidote; *Oximes* are NOT useful.
- *Organochlorines* (*chlorinated hydrocarbons*)—include *DDT*, *Gamma benzene hexachloride (lindane)*; *Cyhalothrins*—*endrin*; *Endrin* is also called *plant penicillin*. Atropin is NOT useful in these cases.

Active Principles of Organic Irritants

Poison	Active principle
Calotropis (madar)	Calotropin, Calotoxin, <i>Uscharin</i> , <i>Gigantin</i>
Semicarpus anacardium (marking nut)	Semicarpol and <i>bhilawanol</i>
Datura	Hyoscyamine, hyoscyne (scopolamine) and <i>atropine</i>
Strychnine	Strychnine, brucine and loganine
Aconite (<i>Mitha vish</i>)	Aconitine
Ricinus communis (Castor)	Ricin
Abrus precatorius (Ratti)	Abrin
Croton tiglium (Jamalgota)	Crotin, Crotonoside
Capsicum annum	Capsaicin

VEGETABLE POISONS

- *Abrus Precatorius (Ratti)*—Seeds are used for *killing cattle* in the form of *sharp needles/arrow poison* called '*suis* (*sin needles*)'. Seeds are also used as abortifacient. Active principle is *abrin*—*resembles viper snake venom*.
- *Ricinus communis (castor)* contains *ricin*, which produces *hemorrhagic inflammation of the GIT* even when given subcutaneously. The powder of seeds causes *conjunctivitis* when applied to the eye.
- *Semicarpus anacardium (marking nut or bhilawan)*—juice applied externally causes a painful blister—used to produce *artificial bruise*; also used by *washerman to mark clothes*; active principles are *semicarpol* and *bhilawanol*.
- *Aconite (Monk's hood, mitha vish/bish or mltha zaher)*—symptoms of poisoning are: *paresthesias of mouth and tongue* (MAIN symptom); hypersalivation; low BP and hypothermia and *hippus*.
- *Croton tiglium* (*jamalgota* or *nepala*)—a *resicating resin*.
- *Cerebra thevetia* (*yellow oleander*)—toxic principles are *thevetin* (main—*cardiac poison*); *thevetoxin* (less potent) and *cerehrin* (*strychnine like*).
- *Nerium Odorum* (*white oleander*)—cardiac poison; toxic principles are *nerin*, *oleandrln*.
- *Calotropis (madar)*—has 3 toxins—*uscharin*, *calotropin* and *calotoxin*; *milky manur juice* has been used for *infanticide* by giving mixed with milk.
- *Gelsemium (yellow or false jussulne)* is a powerful *spinal depressant*.
- *Toxalbumin* or *phyto toxin* is a toxic *protein* that agglutinates RBCs and causes hemolysis and cell destruction (cytolysis). Plant *toxalbumins* are *ricin*, *Abirin* and *crotin*.



Fig. 16.9: Semicarpus anacardium

METHYL ALCOHOL POISONING

- Methyl alcohol (methanol) poisoning results from drinking **methylated spirit** (mixed with **country liquor**).
- Methanol is metabolised to formaldehyde (by alcohol dehydrogenase) and formic acid (by aldehyde dehydrogenase).
- Formic acid accumulation causes toxic effects—**lactic acidosis/high anion gap metabolic acidosis**; blindness due to **primary optic atrophy** (preceded by **papilledema and retinal arterial narrowing**) **bilateral cystic putaminal necrosis seen at autopsy**.
- **Clinically: Vomiting abdominal pain**, confusion, acute loss of vision/blindness.
- Fatal dose in adults is 60–240 mL.
- **Treatment: Gastric lavage; sodium bicarbonate; ethanol** (competitively inhibits aldehyde dehydrogenase); **fomepizole** (specific inhibitor of alcohol dehydrogenase); **hemodialysis**; **folic acid** (hastens metabolism of formic acid).

OTHER CNS DEPRESSANTS

- **Barbiturate poisoning**: CNS depression; cyanosis; hypotension; CVS collapse; **barbiturate blisters**; **constricted pupils**, **gold colored urine**; **hypothermia**; **coma**; treat with **forced alkaline diuresis**.
- **Chloral hydrate poisoning** is also called **Mickey Finn**; **knockout drops**; **dry wine**. A crystalline substance with **pungent odor**; powerful hypnotic causes CNS depression.

Datura (thorn apple) poisoning

- ▶ Two main types are **Datura alba** and **Datura Niger**; active principles are **levahyascyamine**, **hyascine (scopolamine)** and **atropine**—all have **anticholinergic** action.
- ▶ Clinically: **dry 'hat' skin** ('hat as a hare'); **dilation of cutaneous blood vessels causing facial flush** ('red as a beet'); **dilated pupil** ('blind as a bat'); **dryness of mouth** ('dry as a bone'); **delirium** ('mad as a wet hen/hatter'); **dysphagia**; **difficulty in talking**.

Datura (thorn apple) poisoning

- ▶ For treatment, **physostigmine** is the drug of choice.
- ▶ Datura seeds **resemble capsicum seeds**; BUT datura seeds are larger, thicker and kidney shaped.
- ▶ Pilocarpine test: 1% pilocarpine in eye = No constriction
- ▶ Datura stramonium is also called 'thorn apple' or 'jimsonweed'.



Fig. 16.10: Datura seeds

STRYCHNINE POISONING

- Caused by **Strychns nux vomica (kuchila)**; active principles are **strychnine** and **brucine**—neurotoxic.
- Strychnine is used as **cattle poison**, **rodenticide**, **respiratory stimulant**.
- **Mechanism: Strychnine** depresses the inhibitory postsynaptic potentials in the spinal cord and **prevents the effects of glycine** (the inhibitory neurotransmitter). Widespread inhibition in the spinal cord results in 'release' excitation.
- It **stimulates the CNS—cerebral cortex** (esp. **anterior horn cells**) and **respiratory center**.
- **Opisthotonus** (hyperextension of whole body) **emprosthotonus** (abdominal muscle spasm bending the body forward) or to the side (**pleurosthotonus**) may be seen.
- **Consciousness remains clear** till death.
- **FATAL DOSE** of strychnine is 50–100 mg.
- Strychnine poisoning resembles **tetanus**.

Strychnine Poisoning and Tetanus Compared

Trait	Strychnine	Tetanus
Onset	Sudden	Gradual
History	No history of injury	H/o injury present
Convulsions	All muscles of body are affected at same time	All muscles are not affected at same time

Contd.,

33

Trait	Strychnine	Tetanus
Lower jaw	Does NOT start in or especially affect the jaw	Starts in and especially affects the jaw
Muscular condition	Between fits muscles are completely relaxed	Between fits muscles are slightly rigid
Fatal period	1 to 2 hours	More than 24 hours
Chemical analysis	Strychnine found	No poison found

Tests for Strychnine Poisoning

Test	Suspected material (Gastric aspirate/Blood) +
Marshall's test	H ₂ SO ₄ + Cerosorecic acid
Wenzel's test	KMnO ₄ + H ₂ SO ₄

POISONOUS SNAKES

- **Ophitoxemia** = snake poisoning.
- Sea snakes (**Hydrophidae**)—**Myotoxic** (muscle weakness, polymyositis, rhabdomyolysis)
- Viper (**Viperidae**)—**Hematotoxic**, **vasculotoxic** (d/ to phosphatides); causes **oozing of blood** at site of bite; **hematuria** and **hemoglobinuria** occurs due to hemolysis; **Abrus precatorius poisoning** resembles viper bite.

Features of Poisonous (Venomous) Snakes

Trait	Venomous	Non-poisonous
General appearance	Stout, dull colored	Slender, brightly colored
Head	Triangular	Rounded or oval
Head scales	1. Small in viper 2. Large with pit near eye and nostril— pit viper 3. Third labial touches the eye and nasal shield— cobra/ carai snake 4. No pit; 3rd labial does NOT touch the eye and nasal shield; central row of scales on back, enlarged and hexagonal in shape; lower jaw has 4 infralabials, 4th infralabial is largest— Krait	Large with exceptions as mentioned in left side column
Belly scales	Large and cover entire breadth of the belly	Small, like those on the back
Anal plate and subcaudal scales	Single row	Double rows
Teeth	Two long fangs and a row of smaller teeth	Several small teeth arranged in rows but no fangs
Fangs	Canalized like hypodermic needles (vipers) or have grooves (cobra)	NO fangs
Poison glands	Present	Absent
Saliva	Contains toxic polypeptides and enzymes	No
Tail	May be rounded or flattened/ compressed ; tapers abruptly	Always rounded and taper gradually
Habits	Mainly nocturnal	Diurnal

- **Cobra, Krait (Elapidae)**—**Ne(w)urotoxic**. ('My Sea Snakes V(w)ipe Haem With New (CK)obras!').
- Treatment: Do it **RIGHT** mnemonic! **Reassure** patient; **Immobilize** the limb; **Get to Hospital**; **Tell** the doctor of any new symptoms.
- **No local incision**; **No mouth suction**; **No tourniquet** (was used in earlier times, proximal to bitten area); **No ice packs**; **No electric current**.
- **PAV (polyvalent snake antivenin)** is prepared by hyperimmunizing horse against the 4 common snakes, i.e. **cobra** (naja naja); **krait** (bungaris ceruleus); **russel's viper** (daboia russel); **saw scaled viper** (echis carinata).
- The **recommended initial dose of ASV is 8–10 vials** administered over 1 hour.
- **Pressure immobilization for elapid bites** (neurotoxic) is recommended, including sea snakes BUT NOT for viper bites (can cause local necrosis). A compression bandage from the bite site upwards should be wrapped maintaining a **pressure of 50–70 mm Hg**.
- 20 minutes whole blood clotting test (**20 WBCT**)—very useful test.

Fatal Dose of Dried Venoms

Krait	6 mg
Echis	8 mg
Cobra	12 mg
Russell viper	15 mg

SCORPION STING

- *Scorpion venom is more toxic than snake venom*; it delays inactivation of sodium channels of autonomic nervous system resulting in '**autonomic storm**'.
- Its venom contains **neurotoxins** that cause **sodium channels to remain open**.
- Clinically: a/w little swelling, but prominent **pain, paresthesia, and hyperesthesia** can be accentuated by tapping on the affected area (the tap test); **hyperexcitability of skeletal muscles** (muscle twitching, jerking) develop within hours.
- Patients present with **restlessness, blurred vision, abnormal eye movements, profuse salivation, lacrimation, rhinorrhea, slurred speech, difficulty in handling secretions, diaphoresis, nausea, and vomiting**.
- Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, and acidosis. Fatal respiratory arrest is most common among young children and the elderly.

CARBON MONOXIDE (CO) POISONING

- CO causes **anemic hypoxia**.
- **Carboxyhemoglobin** of 40-50% resembles alcohol intoxication; > 80% causes death from respiratory arrest.
- **Upper limit of safety** of CO in air is **0.01%**.
- Causes **cherry red discoloration** of blood and tissues.
- Symptoms start when concentration exceeds 10%.
- Bilateral symmetrical **necrosis and cavitation of basal ganglia** (esp. putamen and globus pallidus) is seen—may be confused with **Parkinson's disease**.

Tests for CO Poisoning

Test	Suspected material (gastric aspirate/blood) +
Kunkel's test	Tannic acid
Hoppe-Seyler's test	Sodium hydroxide
Wetzel's test	Tannic acid + potassium ferrocyanide
Katayama's test	Yellow ammonium sulfide and acetic acid
Liebmann's test	Formaldehyde
Rubner's test	Basic lead acetate
Haldane's carmine	Color after dilution

MORE HIGH YIELD POISON FACTS

- In **methyl isocyanate poisoning** (Bhopal Gas), acute irritation of eyes, lacrimation, blurring of vision, severe

burning of throat, chest pain and pulmonary edema are seen.

- **Spanish fly (blister beetle or cantharides)** bite causes **priapism**. Powder of the dried body of this beetle (**cantharedin**) causes **vesication**.
- Spleen is ruptured usually on its **concave** surface.
- Chronic iodine poisoning is **iodism**.
- **Chlorine poisoning**, death is caused by **cardiac failure**.
- Common salt decomposes **silver nitrate**.
- **Universal antidote** consists of powdered animal charcoal (or burnt toast) 2 parts; magnesium oxide 1 part; tannic acid or strong tea 1 part.
- **Fruit with bite mark** should be preserved in **Campden's solution** (**metabisulfite** fluid).
- Even if **tattoo mark** has disappeared from the skin, the dye may remain in the regional **lymph nodes**.
- **Sewer gas** = $\text{H}_2\text{S} + \text{CO}_2$ + methane.
- **Marsh gas** = **methane**.
- **Conium** (**hemlock**) was used to **kill Socrates**.
- Conjunctiva and cornea are grey/black in **silver poisoning**.
- **Marquis reagent** = formaldehyde + sulfuric acid; gives purplish color with morphine and orangish brown with amphetamines.
- **Scott test**—cobalt thiocyanate reagent—for testing for cocaine.
- **Dille Koppanyi test**—for barbiturates.
- **Duquenois Levine test**—for marijuana.
- **Van Urk reagent** test—for LSD.
- Conium is a peripheral poison.
- In **potassium permanganate poisoning**, lesions resemble **tertiary syphilis**.
- **Magenstrasse**—pathway that acidic agents follow in the stomach.
- The extracellular forms of **phospholipases A2** have been isolated from different **venoms** (**snake, bee, and wasp**).
- **Gila monster** is a **venomous lizard**.
- Specimen containing **viral particle** is preserved in **50% glycerine**.
- **Dialysis dementia syndrome** is seen in **aluminium poisoning**.
- As per Motor Vehicle Act 1988, driving with blood alcohol level > **30 mg/100 mL** is considered as **drunken driving**.
- **Erythematous desquamating rash**—'**boiled lobster**' skin—seen in **boric acid toxicity**.
- **Automatism** can lead to accidental **barbiturate poisoning**.

CHAPTER

17

Ophthalmology

EMBRYOLOGY OF EYE STRUCTURES

Surface Ectoderm	Neural Ectoderm	Neural Crest
<ul style="list-style-type: none"> • Lens • Conjunctival epithelium • Corneal epithelium • Lacrimal glands • Tarsal glands (Meibomian, Zeis, Moll) • Skin of eyelids and eyelashes 	<ul style="list-style-type: none"> • Smooth muscles of iris (Sphincter and Dilator pupillae) • Iris epithelium and Ciliary epithelium • Retina and retinal pigment epithelium • Optic Nerve • Optic vesicle and cup • Part of vitreous 	<ul style="list-style-type: none"> • Corneal stroma, keratocytes and corneal endothelium • Trabecular meshwork endothelium • Melanocytes Iris stroma • Ciliary muscles • Choroidal stroma • Part of the vitreous • Meningeal sheaths of the optic nerve • Ciliary ganglion • Schwann cells of the ciliary nerves • Orbital bones • Orbital connective tissue • Connective tissue sheath and muscular layer of ocular and orbital blood vessels • Sclera (maximally)
Mesoderm		
<ul style="list-style-type: none"> • Extraocular muscles • Sclera (temporal small portion) • Iris • Choroid • Vascular endothelium of eye and orbit • Part of Vitreous 		

BASICS OF REFRACTION

Reduced Eye

- To understand the focusing mechanism of the eye as an optical device, **Listing** in 1853 introduced the concept of **reduced eye** (an imaginary single ideal spherical refracting surface) whose **radius of curvature is 5.73 mm** and **refractive power is + 58.6 D**

Refractive Index of aqueous	1.34
Refractive Index of cornea	1.37
Refractive index of lens	1.39
Power of cornea	+ 43-45 D
Power of lens	+ 15-17 D
Power of eye (total)	+ 58-60 D
Power of eye at birth (eye is hypermetropic)	+ 2.5 D

Other Key Points

- **Axial length of adult eye** = 24 mm = length of external auditory canal.

- As seen in table above **most important refracting surface of eye** (which provides **maximum refraction/convergence** of light rays) is the **cornea** (anterior surface).
- **Purkinje-Samson Images** (**Captotric images**) result from reflections from the refracting surfaces within the eye. There are 4 images—
 - **PI** (**anterior corneal** surface)
 - **PII** (**posterior corneal** surface)
 - **PIII** (**anterior lens** surface)
 - **PIV** (**posterior lens** surface - **inverted image**).
- Images **PIII and PIV** are **absent in aphakia**.
- If the axial length of the eye is changed by **1 mm**, then the power changes by **3 Dioptres**.
- In the clinic, normally **distance vision** is measured at a distance of **6 metres**.

Retinoscopy

- A.k.a **shadow test, skiascopy, korescopy**
- Retinoscopy is the **determination of refractive state of the eye**.

- Types of retinoscopy are
 - Spot retinoscopy
 - **Streak** retinoscopy (*preferred*)

Retinoscopy with Plane Mirror at 1 Distance:

- Reflex moves in **same direction** in: **emmetropia, hypermetropia and in myopia < 1D**
- Reflex moves in **opposite direction** in: **myopia > 1D**
- **NO** movement of red reflex in: **myopia of 1D** (reflex neutralized)

- **Refractive error** = Retinoscopic reading MINUS deduction for distance at which retinoscopy is done (1D for 1m and 1.5D for 66 cm) MINUS deduction for types of drps used (1D for atropine, 0.75D for cyclopentolate and 0.5D for homatropine).

Mydriatics and Cycloplegic Drugs

- Mydriasis: Dilatation of the pupil
- **Cycloplegia means paralysis of accommodation** (ciliary body).
- All mydriatics have some cycloplegia except phenylephrine

Drug	Duration of effects
Tropicamide (1%)	Lasts for 4-6 hours; shortest acting mydriatic
Cyclopentolate (1%)	Lasts for 1 day
Homatropine (2%)	Lasts for 3 days
Atropine (1% ointment)	Lasts for 10 days; longest acting mydriatic
Phenylephrine (5-10%)	ONLY mydriatic effect, NO cycloplegia

Eyedrops for Retinoscopy

- If the **child is < 5 years**, **atropine eye ointment 1%** is used as cycloplegic. **Ointment preferred over drops** since drops can lead to more systemic absorption and cause facial flushing, fever and other side effects of atropine.
- If the patient is **between 5 and 20 years**, **1% cyclopentolate or 2% homatropine eye drops** is used as cycloplegic.
- **For adults (> 20 years)**, tropicamide with phenylephrine combination or pure phenylephrine is used (cycloplegia usually NOT required).

REFRACTIVE ERRORS

Myopia vs Hypermetropia

Myopia (short sight)	Hypermetropia (Far sightedness)
Eyeball is large – light gets focused in front of (anterior) to retina –corrected by placing concave (minus / diverging) spectacle lenses	Eyeball is small – lights gets focused behind the retina –corrected by placing convex (plus) spectacle lenses
Distance vision is defective; Child squeezes eyes to see distant things clearly	Both near and far vision are defective; Latent hypermetropia is revealed by cycloplegic refraction
Fundus findings Large optic discs; Posterior staphyloma; Lattice degeneration; Chorioretinal atrophy; Peripapillary atrophy (temporal crescent); Foster Fuch's spots at macula; Lacquer cracks in retina	Fundus findings Small crowded optic disc – pseudopapillitis Prominent shiny retinal nerve fibre layer – silkshot retina
Complications Retinal detachment; Predisposes to POAG	Complications Predisposed to PACG; Early presbyopia; Degenerative retinoschisis

EXTRA EDGE

- **Myopia** is the **MC** refractive error.
- **Simple myopia** — power is about 5-6 D and stops increasing by 21 years.
- **Pathological myopia** — Large axial length, power increases even beyond 25 years and may be minus 15 to 25 dioptres; degenerative changes in fundus appear later during 5th decade; MC in women, Jews and Japanese; there maybe an **apparent convergent squint**.

Treatment of Hypermetropia

- Spectacles OR contact lenses
- **Conductive keratoplasty (Holmium YAG laser thermokeratoplasty)**
- **Hyperopic LASIK** (+1 to +4 D)
- **Phakic IOL** (+6 to +10 D)

Treatment of Myopia

Procedure	Range of Myopia
Spectacles (concave) OR contact lens	Any range
Radial keratotomy	1-6 D

Contd.

Procedure	Range of Myopia
INTACS (Intracorneal ring segments)	1-6 D
Excimer laser photorefractive keratectomy (PRK)	1-4 D
LASIK (see under cornea chapter)	2-12 D
LASEK (see under cornea chapter)	1-6 D
Clear lens extraction (Fukala's)	> 15 D
Phakic IOL	> 12 D

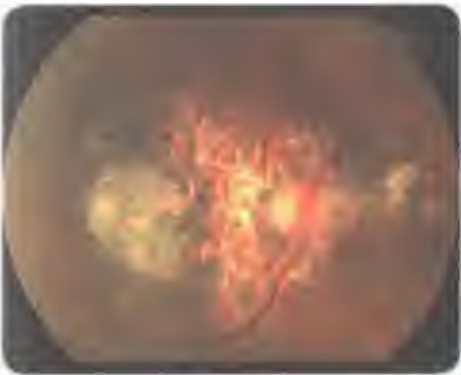


Fig 17.1: Lacquer cracks with Foster Fuch's spot at macula

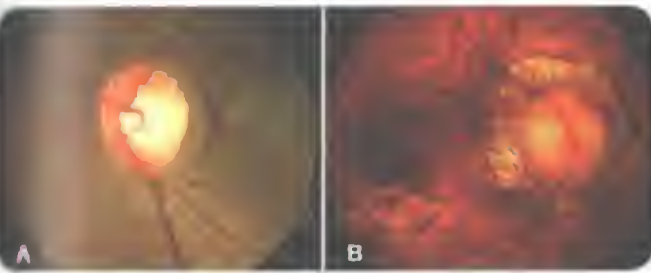


Fig 17.2A and B: Fundoscopic findings in myopia. A. Temporal crescent



Fig 17.3: Hypermetropic fundus—pseudoneuritis and shot-silk appearance

Astigmatism

- Here the cornea is not a uniform spherical surface and is **curved differently in different meridians**.
- When the cornea has its greatest and least curvatures at **right angles to one another** it is called **regular astigmatism**.
- In the commonest form, the **vertical meridian is more curved**, the condition is called – “**with the rule**”; the reverse is said to be “**against the rule**”.
- If the corneal surface is irregular (such as opacity after corneal ulcer), different rays of light are refracted irregularly to form foci in different positions – **Irregular astigmatism**.
- In **simple astigmatism**, **one image is formed upon retina** (i.e. one meridian is emmetropic) and the **other image may be formed behind or in front of the retina** (i.e. other meridian is either hypermetropic or myopic). These are designated as simple hypermetropic and simple myopic astigmatism respectively.
- In **compound astigmatism**, **both images are formed either in front (k/a compound myopic astigmatism) or behind retina** (k/a compound hypermetropic astigmatism).
- In **mixed astigmatism** **one image is formed in front and other behind the retina**.
- A regularly astigmatic surface is said to have a “**toric**” curvature.
- The more curved meridian will have greater refractive power than the less curved meridian; so if parallel rays fall upon such a cornea, vertical rays will come to focus sooner than the horizontal. Thus the rays will have two foci – this entire bundle of rays is called **Sturm's conoid**.
- **Jackson's cross cylinder**: **One plus cylinder and one minus cylinder** with their axes at right angles to each other; available in power of 0.25 and 0.5.

Aphakia

- Absence of the natural crystalline lens from the eye is aphakia.
- However, optically absence of lens from its position on the pupillary area is also considered aphakia.
- **Causes of aphakia**: Surgical (MC post ICCE surgery in olden days); posterior dislocation of lens, traumatic self absorption of lens, congenital absence etc.
- **Signs of aphakia**: **Deep anterior chamber, Jet black pupil, iridodonesis, only 2 Purkinje's Images seen**.

• **Treatment of Aphakia:**

➤ **Best treatment is PCIOL** (Posterior chamber Intraocular lens - *in the capsular bag* as is done in modern day cataract surgery). If capsular bag is not intact/absent, then **scleral fixated IOL (SFIOL)** procedure can be done.

➤ **Spectacles:** high powered **convex (plus)** lenses; very heavy, **image is magnified** by 30% - causes **aniseikonia** (difference in the size of the image formed by the two eyes); **pin-cushion effect** (due to spherical and chromatic aberration); **roving-ring scotoma** and **jack-in-the-box** phenomenon (prismatic effect at edge of lens).

➤ **Contact lenses:** better preferred than spectacles.

Presbyopia

• **Presbyopia** is a condition of physiological *insufficiency of accommodation* in which *near point gradually recedes beyond* the normal reading or working distance, leading to **failing vision for near**.

• **Difficulty in reading/near work** and "arms are not long enough" (to hold the newspaper farther) are common symptoms.

• Treat with appropriate **convex lenses** (for near addition - *no cycloplegia required in adults*).

• A rough rule of thumb to provide corrective lenses for near vision is as below:

- + 1.0 Dioptres for 40 years age
- + 1.5 for 45 years
- + 2.0 for 50 years
- + 2.5 for 55 years
- + 3.0 for 60 years

Aberrations

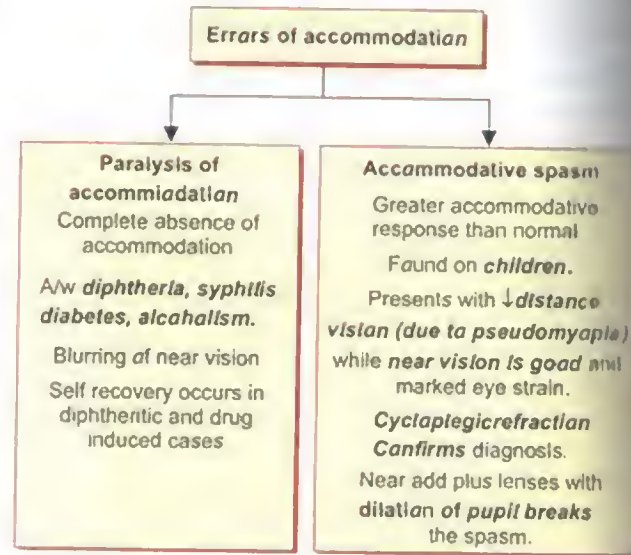
• **Spherical aberration:** **Blurring of the edges of the image** - the **iris reduces this** to a minimum.

• **Chromatic aberration:** When white light is refracted at any surface, its gets split up into all colors of the spectrum; **violet is refracted most and red the least**, the image will have colored edge; in the eye this effect is **very minimal**.

• In the eye, the **natural mechanisms to counteract aberrations** include:

- The **cutting off of peripheral rays by the iris**
- The **high refractive index of the core of the lens nucleus** than peripheral cortex
- **Reduced sensitivity of the peripheral retina**

➤ The **Stiles Crawford effect** or the **greater sensitivity of retinal photoreceptors to perpendicular** than oblique rays.



Spectacle Lenses

• **Glass lenses:** Refractive index 1.52; **Crown glass** used *do not scratch easily*.

• **Plastic lenses:** Made of CR39 (**CR=Columbia Resin**); **lighter** than glass; *do not shatter BUT* easily scratched and warped.

• **Polycarbonate:** *Very light and thin, high refractive index; scratch resistant and unbreakable*; offer total UV protection; 10 times stronger than plastic - ideal for **children and sports persons**.

• **Photochromatic lenses:** Darken in sunlight by conversion of **silver ions into elemental silver** in glass lenses (Plastic lenses incorporate organic molecule); the reaction is reversible.

• **ARC = Anti reflective coating;** reduces glare from headlights and computer screens.

• **High Index lenses:** Refractive Index of **1.56 to 1.67**. Lenses are **thinner, flatter and lighter** and provide **cosmesis for very high refractive errors**.

• **Aspheric lenses:** Have curves that flatten away from the centre **limiting diffraction**; specially **designed for hypermetropes** who otherwise will need thick lenses.

• **Bifocal lenses:** For both **near and distance vision**.

• **Multifocal lenses** for near, intermediate and distance vision (**progressive lenses**).

• Normally after cataract surgery spectacles are prescribed after **6 weeks**.

Contact Lenses

	Hard	Soft	RGP
Material	PMMA (polymethyl methacrylate)	HEMA (hydroxyethyl methacrylate)	Copolymer of PMMA, silicone and CAB
Delivery	Poor	High	Moderate to high
Visual clarity	Good	Need to refocus after a blink	Clear vision
Use for astigmatism	Yes	Less suitable	Yes
Adaptation	Required	Not required	Required
Deposits	Few	Accumulate over time	Few

Contd...

Contd.

	Hard	Soft	RGP
Durability	May scratch	Tend to tear	Do not scratch or tear

CAB = cellulose acetate butyrate; RGP = Rigid Gas Permeable

EXTRA EDGE

- **Toric contact lenses:** Both soft and RGP lenses are available for **astigmatism**.
- **Rose K lens:** special type of contact lenses **specifically for keratoconus**.
- **Boston and Jupiter scleral lens:** **Gas permeable scleral contact lenses**, for patients with corneal disease, including **keratoconus, Stevens-Johnson syndrome**.
- **Orthokeratology:** Refers to **reshaping of the cornea by wearing contact lenses overnight**; useful for mild myopia and astigmatism.

REFRACTIVE PROCEDURES

Procedure	Method	Comments
Laser In Situ keratomileusis (LASIK)	Make epithelial flap with microkeratome , selectively ablate corneal stroma with Excimer (193 nm) laser , replace flap; no sutures, it sticks by itself	Less painful, faster visual rehabilitation. NOT suitable for thin corneas. Diffuse lamellar keratitis (sands of Sahara syndrome)
Laser Sub-Epithelial keratomileusis (LASEK)	Remove epithelium as a sheet with 20% alcohol, ablate stroma with excimer laser , replace epithelium, insert bandage contact lens	Useful in thin corneas
Epi LASIK	Remove epithelial sheet with epikeratome , ablate stroma with excimer laser , replace epithelium, insert BCL	Useful in thin corneas
Femtosecond laser assisted LASIK (Wavelight)	Femtosecond laser (1053 nm) is used to create flap, NOT blade	Hence Bladeless LASIK
Photo-refractive keratectomy (PRK)	Remove epithelium by blade, spatula, burrs, laser or alcohol; selectively ablate stroma with excimer laser , insert BCL	Advantages over LASIK: No issues of flap stability (important for military, contact sports), Disadvantages: Postop pain, slow recovery
Thermokeratoplasty (conductive keratoplasty)	Local heat induced shrinkage of corneal tissue results in corneal steepening	Holmium laser; To treat mild degrees of hypermetropia and presbyopia
SMILE	Small Incision Lenticular excision	Femtosecond laser is used No flap is created

EXTRA EDGE

- EXCEPT thermokeratoplasty in above table; **+4D to -8D Spherical** and upto **4D of astigmatism** is the indication for the procedure.

BCL = Bandage Contact Lens.

LASIK

Indications

- Approved range for myopic correction is **+4D to -10D Spherical** and upto **4D of astigmatism**.
- Residual stromal bed thickness should be **at least 250 microns**.
- Hyperopic corrections have been approved for **+4.00**.

Contraindications

- Unstable refractive error (i.e. **changing spectacle power**).
- **Age less than 18 years**.
- Active **collagen vascular disease** + iritis or scleritis.

- **Pregnancy; Pacemaker** (older generation).
- Any **ongoing active inflammation** of the external eye (e.g. conjunctivitis, severe dry eye).
- **Keratoconus** or any condition which thins the cornea - **absolute contraindication**.

Newer LASIKs

- ▶ Bladeless LASIK: **Femtosecond laser** is used for flap creation.
- ▶ Enhancement LASIK: (i.e. **repeat procedure**) can be performed but usually after 3 months of stable refraction
- ▶ Wavefront LASIK: Aims to **correct all aberrations of the eye** to give vision beyond 6/6 – supervision

INSTRUMENTS/TESTS

- **Retinoscopy** Objective method of determination of refractive error of eye
- **Gonioscopy** To view angle of anterior chamber
- **Pachymetry** Measures thickness of cornea
- **Keratometry** To measure the curvature of the cornea
- **Campimetry / Perimetry** Measures field of vision
- **Specular microscope** For **corneal endothelial** cell count and endothelial study
- **Confocal microscope** To study corneal layers, useful in acanthamoeba keratitis
- **Tonography** measures **facility of outflow of aqueous**
- **OCT, HRT**
 - OCT= Optical coherence tomography; HRT = Heidelberg Retina Tomogram
 - To study retinal nerve fibre layers, useful in glaucoma and macular pathology
- **GDX** To study retinal nerve fibre layers – used in glaucoma only
- **Corneal topography** To study corneal surface; done to diagnose keratoconus, done prior to LASIK
- **Placido's disc** For corneal topography/corneal surface regularity
- **UBM (Ultrasound biomicroscope)** To view angle structures and to classify the type of glaucoma; useful in opaque corneas to view anterior segment structures and upto 5 mm depth
- **B scan ultrasound** For posterior segment evaluation (vitreous and retina; can also see optic nerve cupping and extraocular muscle thickening) (**B = Brightness**)
- **A scan ultrasound** For Axial length calculation which is used in IOL power calculation before cataract surgery
- **Potential Acuity Meter** To check the possible visual acuity after cataract surgery in dense/mature cataracts
- **Amsler grid** To detect maculopathy and macular degeneration; to assess macular status
- **Optokinetic nystagnus** Best elicited with optokinetic drum which has black and white vertical stripes painted on it. As the drum rotates, the patient fixates on the stripes. There is a slow phase towards the direction of movement of the drum and when the stripes go out of the field of view, the eyes have a fast phase so that they come back to the centre and refix at the new stripes once again.
- **Photostress test** Positive In early macular disease (esp. central serous retinopathy); recovery time at least 1/3 longer than recovery time of a normal person is considered significant
- **Snellen's chart** **Distance** vision is measured at a distance of **6 metres** using **Snellen's** chart.



Fig. 17.4: Streak retinoscope

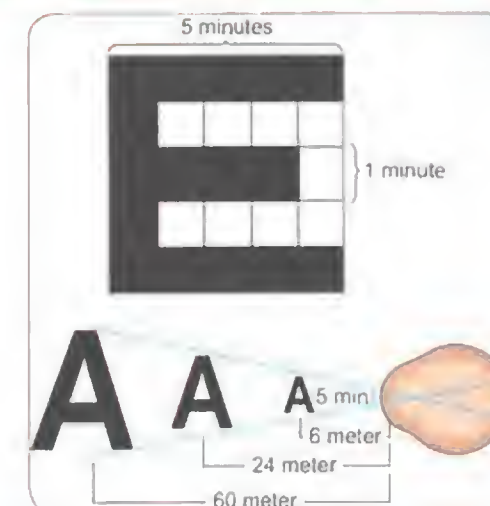


Fig. 17.7: Construction of the Snellen letter. Each part subtends an angle of 1 minute. Whole letter subtending an angle of 5 minutes at varying distance from the eye



Fig. 17.5: Slit lamp biomicroscope



Fig. 17.8: Specular microscopic photography. Normal endothelial cells

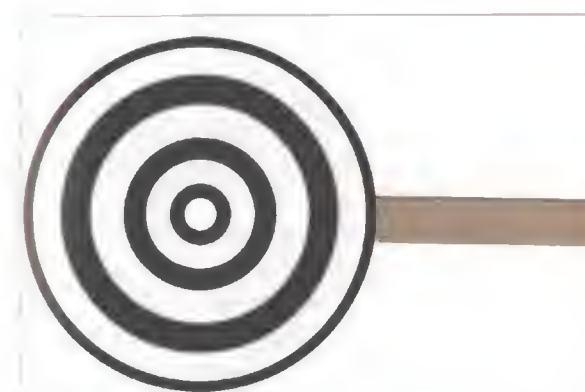


Fig. 17.6: Placido disc

OPHTHALMOSCOPY

Direct ophthalmoscopy	Indirect ophthalmoscopy
Distant direct: From 25 cm distance.	From about 1 m distance (+20 D Lens is used)
Near Direct ophthalmoscopy: From very close to patient's eye (within 1-2 cm)	
Hand held instrument, self illuminated	Worn on the head with head band, self illuminated
Erect, Virtual image	Inverted, Real image

Contd...

Direct ophthalmoscopy	Indirect ophthalmoscopy
Magnified 15 times ("DEV15")	Magnified 5 times
Area of field in focus is 2 Disc Diameters (2 DD)	Area of field in focus is 8 DD
Useful to see posterior pole, i.e. optic disc and macula/fovea, cannot see periphery	Useful to see periphery, ora serrata, vitreous base (posterior pole also), esp. in retinal detachments and degenerations
Less illumination, difficult to use when cataract is present	Bright illumination, can see through cataracts
No stereopsis	Good stereopsis (i.e. depth perception) - elevations/depressions (as in retinal detachments) can be made out



Figs. 17.9A and B: A. Direct ophthalmoscope; B. Procedure of direct ophthalmoscopy



Figs. 17.10A and B: A. Indirect ophthalmoscope with lens; B. Procedure of indirect ophthalmoscopy

CONJUNCTIVA

Basics

- Stratified *non-keratinised stratified squamous columnar epithelium*.
- *Goblet cells* chief source of *mucus* in tear film they are *most dense nasally (esp. inferonasally)*.
- *Lymphatic drainage of lateral conjunctiva* is into *preauricular nodes* and *medial side* into *submandibular nodes*.
- The *adenoid superficial layer* (lymphoid layer) of conj stroma does NOT develop until 3 months after birth - hence *inability of newborn to produce follicles till 2-3 months of age*.
- *Plica semilunaris* is a pink crescent shaped fold of conjunctiva present in medial canthus—vestigial structure in humans representing the *nictitating membrane (third eyelid)* of lower animals.
- Subconjunctival hemorrhage (in conjunctivitis) occurs due to: *Acute hemorrhagic conjunctivitis, (picornavirus-enterovirus 70, coxsackie A virus 24),*

Conjunctival True membranes	Conjunctival pseudomembranes
Infiltrate superficial layers of conjunctiva and removal causes tearing of the epithelium and bleeding	Can be easily peeled off (no bleeding) leaving the epithelium intact
<ul style="list-style-type: none">• Diphtheria; Gonococcal conjunctivitis• Acute Steven Johnson syndrome• Severe adenoviral conjunctivitis	<ul style="list-style-type: none">• Adenovirus• Bacterial (Staphylococcus, Streptococcus, N.meningitidis, Pseudomonas, coliforms)• Chemical burns, foreign bodies, pemphigoid, liginous conjunctivitis



Fig. 17.11: Pseudomembrane

Acute Red Eyes

	Acute conjunctivitis	Acute iridocyclitis / uveitis	Acute angle closure glaucoma	Corneal abrasion/infection
Vision	Normal	Blurred	Markedly blurred	Blurred
Discharge	Moderate to copious	None	None	Watery
Pain	Mild	Moderate	Severe	Moderate
Congestion	Conjunctival	Ciliary	Ciliary	Ciliary
Cornea	Clear	Clear, KPs may be seen	Steamy/hazy/edematous	Related to cause
Pupil	Normal size and reaction	Small and sluggish/irregular	Mid dilated, vertically oval and fixed	Normal size and reaction
IOP	Normal	Acutely low, later high	Very high with nausea and vomiting	Normal
Smear	Causative organisms	None	None	In cases of corneal infection

Conjunctivitis

Conjunctivitis	Features	Treatment
Bacterial conjunctivitis	Staphylococcus aureus (<i>corneal margins and lid margins involved</i>), Streptococcus pneumonia and H.influenza (<i>subconj. hemorrhage</i> occurs). <i>Mucopurulent discharge, sticky eyes, mottled eyelashes, papillae</i>	Topical antibiotic drops and ointments
Viral conjunctivitis	Adenovirus (<i>pink eye</i>), Herpes simplex, picornavirus <i>Watery discharge, subconjunctival hemorrhages, follicles, pre-auricular lymphadenopathy</i> , lasts for longer time	Cold compresses, lubricant eyedrops, antibiotic drops to prevent bacterial superinfection; <i>occupational hazard</i> of ophthalmologists
Adenoviral keratoconjunctivitis	"Pink eye", Signs as above; <i>occupational hazard for ophthalmologists; Epidemic keratoconjunctivitis - serotypes 8,19,37; severe infection can leave anterior stromal infiltrates</i> that fade over months	Keratitis responds well to <i>topical steroids</i> ; conjunctivitis - treat as above. Note: steroids ARE used here.
Liginous conjunctivitis	MC in children/young adults; unknown etiology ' <i>woody membrane</i> ' over conjunctiva	<i>Surgical removal</i> of membranes - tends to recur; topical cyclosporine, hyaluronidase or corticosteroids
Angular conjunctivitis	MC and classically due to <i>Moraxella lacunata (gram negative diplobacillus)</i> ; also by <i>Staph aureus</i> ; at risk - <i>chronic alcoholism, malnutrition</i>	Treat with <i>zinc oxide</i> containing eye drops

Contd

Contd....

Conjunctivitis	Features	Treatment
Phlyctenular conjunctivitis	Type IV hypersensitivity reaction to endogenous tuberculin or to staphylococcal blepharitis ; small pinkish nodule on conjunctiva	Treat with topical antibiotic ointment; corticosteroid drops
Giant papillary conjunctivitis	Due to mechanical trauma (exposed sutures, prosthesis, filtering bleb) or hypersensitivity to contact lens wear (soft CLs > Rigid/hard CLs); ' giant ' papillae > 1 mm dia.	Remove mechanical irritation; change/refit contact lenses; topical anti-allergics or topical corticosteroids
Superior limbic keratoconjunctivitis	A/w Grave's disease of thyroid ; Pain, redness watering; Superior bulbar conjunctival congestion, corneal pannus and filamentary keratitis	Lubricant eyedrops, cyclosporine eyedrops; silver nitrate on cotton bud for 1-20 second followed by thorough irrigation and antibiotic ointment
Parinaud's oculoglandular conjunctivitis	MC in children , usually unilateral ; granulomatous nodules and follicles on palpebral conjunctiva ; fever; swollen preauricular and submandibular node	MC due to Bartonella henselae – Cot Scratch disease ; Others: tularemia, TB, lymphoma, sarcoid, syphilis. Systemic antibiotic as per cause
A. israelii conjunctivitis	Chronic unilateral congestion at medial angle of eye with infection of lacrimal system	Pressure on canaliculus may express whitish granular matter
Acute hemorrhagic conjunctivitis	Caused by Adenovirus and Picornaviruses – Coxsackie A 24 and Enterovirus 70;	

Vernal Kerato-conjunctivitis (VKC)

- A.k.a. Spring Catarrh since commoner in **spring season** and warm climates.
- Affects **children/young adults**; **type I hypersensitivity reaction** due to external allergens; intense **itching**, mucoid '**stringy/ropy**' discharge — (**Maxwell Lyon sign**); **cobblestone papillae** on undersurface of upper eyelid; **Horner-Tranta spots** at limbus; corneal '**shield ulcer**' may be seen; **pseudogonorrhea** (also called '**cupid's bow**', **peripheral corneal scar** resembling **arcus senilis**); **alkaline tears**
- Treatment: **Mast cell stabilizers** (sodium cromoglycate, **olopatadine**); limited topical corticosteroids; topical **cyclosporine**; cool compress.

EXTRA EDGE

- VKC patients have incidence of **keratoconus**; also a/w **h/o atopy**



Fig. 17.12: Cobblestone papillae



Fig. 17.13: Horner-Tranta's spots

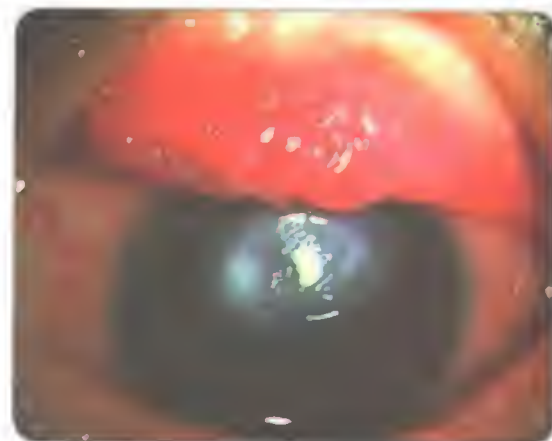


Fig. 17.14: Vernal keratoconjunctivitis—shield ulcer

TRACHOMA

Etiology

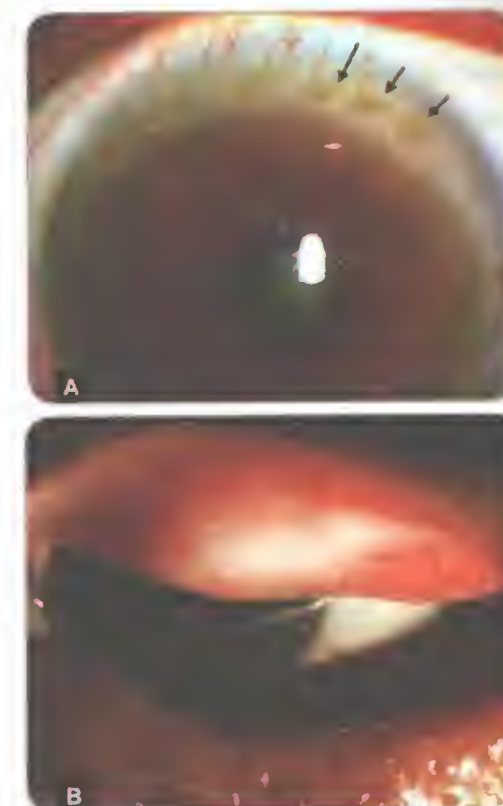
- Caused by **Chlamydia trachomatis serotypes A–C**; transmitted by **direct contact with fomites**: eye secretions, using same towels and by flies; (Note **serotypes D–K** cause **inclusion conjunctivitis – chronic follicular conjunctivitis**).

Clinically

- Farsal follicular reaction, in children < 2 years papillae predominate, **scarred limbal follicles (Herbert's pits)**, **conjunctival scarring (Arlt's line on upper tarsal conjunctiva)**, **entropion**, **trichiasis**, **pannus**, **corneal scarring**; **follicles > 5 mm** usually found **ONLY** in trachoma.
- WHO grading: (**FISTO**)
 - **TF**: Follicular trachoma (5 or more follicles of at least 0.5 mm dia should be present in upper tarsal conjunctiva)
 - **TI**: Intense Inflammation
 - **TS**: Trachomatous Scarring
 - **TT**: Trichiasis
 - **CO**: Corneal Opacity

Treatment and Prevention

- Treat with **Single oral dose Azithromycin** or **tetracycline eye ointment for 6 weeks**.
- SAFE** strategy by WHO for controlling trachoma: **S** (Surgery for trichiasis); **A** (Antibiotics); **F** (Facial cleanliness); **E** (Environmental hygiene).



Figs 17.15A and B: A. Herbert's pits at the limbus (black arrows); B. Trachoma scar

OPHTHALMIA NEONATORUM

- Conjunctivitis in newborn **within the first 4 weeks** postpartum is called **ophthalmia neonatorum**; MC cause is **Chlamydia trachomatis** (serotypes D-K).

Agent	Time of onset	Comments
Chemical	First 36 h	<ul style="list-style-type: none"> Secondary to instillation of Silver nitrate (Crede's method), povidone-iodine or erythromycin – all used for prophylaxis; Bilateral, serous/mucoid discharge, conjunctival hyperemia; Self limited
Neisseria gonorrhoeae	24–48 h	<ul style="list-style-type: none"> Bilateral, copious purulent discharge, eyelid edema, chemosis; corneal ulceration and perforation can occur; Treat with IV ceftriaxone and penicillin plus saline lavage
Bacterial (Staph, Pneumococcus, Haemophilus)	2–5 days	<ul style="list-style-type: none"> Conjunctival congestion, lid edema, chemosis, discharge Erythromycin eye ointment, tobramycin or fluoroquinolone eyedrops
Chlamydia trachomatis D-K	5–14 days	<ul style="list-style-type: none"> Uni/Bilateral, mucopurulent discharge, conjunctival hyperemia, Unlike adults, no follicles in newborns till 8 weeks of birth, since they lack lymphoid tissue; treat with ORAL plus topical erythromycin.
Herpes simplex virus	6–14 days	<ul style="list-style-type: none"> Watery blepharocconjunctivitis, corneal involvement, systemic manifestations

Conjunctival Degenerations

Pinguecula

- Means "fatty"; **Yellow elevated triangular nodule** adjacent to limbus, usually **nasally**; **Elastotic degeneration** of collagen and fibrovascular proliferation; May become inflamed; Treat with artificial tears.

Pterygium

- Means "wing"; Fleshy **bulbar** conjunctival proliferation, usually **begins nasally** and can encroach onto cornea; **Degeneration of the collagen** with thinning of the overlying epithelium and occasional calcification; may become inflamed, grow over visual axis - causes **blurring due to astigmatism**;
- Treat with artificial tears; NSAID drops; surgery involves **excision with conjunctival autografting**; earlier **bare sclera technique** was used and bare area treated with **mitomycin C** eyedrops.

EXTRA EDGE

Recent advances

- Fibrin glue** is being used for **conjunctival outgraft adhesion** in pterygium surgery. Fibrin glue has two components - one is a **fibrinogen** sealant and other is **thrombin** - mixing the two promotes clotting and formation of fibrin cross linking.

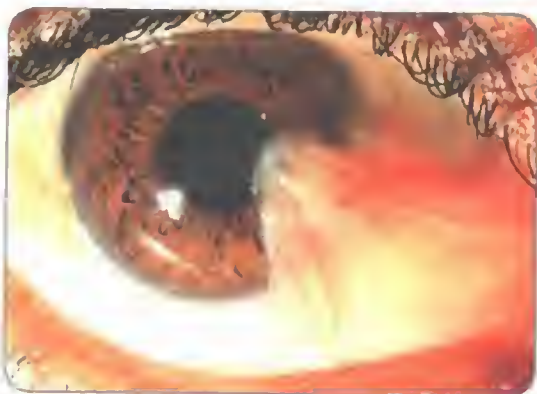


Fig. 17.16: Pterygium

Conjunctival Tumors

- Limbal Dermoid**: usually in **inferotemporal quadrant** of limbus; can involve cornea also; can have hair also; **Goldenhar's syndrome** = limbal dermoid + eyelid colobomas + **preauricular skin tags** + vertebral anomalies.
- Lymphoma**: middle aged affected; light pink **salmon colored** lesion in conjunctiva; complete excision is necessary.

- Malignant melanoma**: middle aged to elderly patient; nodular brown mass; well vascularised; **large feeding vessel** present.



Fig. 17.17: Limbal dermoid

CORNEA

Corneal Basics

	Corneal diameter (mm)		Radius of curvature	Power
	Horizontal >>	Vertical		
Anterior surface	11.7	10.6	7.8 mm	+49D
Posterior surface	11.7	11.7	6.5 mm	-6D

- Corneal thickness (pachymetry)**: Central (**thinner**) 0.5-0.6 mm; Periphery (**thicker**) = 1.2 mm.
- Microcornea** ≤ 10 mm; **MEGALOCORNEA** ≥ 13 mm.
- Corneal power** = 43 - 45D — it is most important refractive surface of the eye especially the anterior corneal surface
- Refractive index** of cornea = 1.37.

Layers of the Cornea

- Anteriorly, **Stratified squamous non-keratinised** epithelium.
- Bowman's layer** (once eroded, it **DOES NOT** regenerate)
- Substantia propria** (stroma - 90% thickness of cornea) contains uniformly spaced **Collagen lamellae** (**mainly type 1 collagen**) lying **parallel** - responsible for **corneal transparency**; **keratocytes** present in stroma; **Long spacing collagen** is sometimes seen in older human corneas.

- Descemet's membrane** (readily **regenerates** after injury; very resistant to chemicals, trauma, infection)
- Endothelium** — most **metabolically active layer**; maintains the deturgescence of cornea; endothelial Na^+/K^+ ATPase pump limits fluid entering the cornea from the aqueous.
- Mnemonic - "ABCDE"

EXTRA EDGE

Recent advances

- Dua's layer**: **Between Stroma and Descemet's membrane (pre-Descemet's)**; newly discovered 15 microns thick layer of cornea.

Factors responsible for corneal transparency

Anatomical

- Avascular**; **Unmyelinated** nerve fibres; **Uniform spacing** of collagen fibrils in stroma (**Maurice theory** - interfibrillar spacing is **less than wavelength** of light; **Galdman and Benedek theory** - stromal fibrils are small and do not interfere with light)
- Uniform refractive index** of all layers
- Epithelium with **high mitotic figures** (which ensures rapid wound repair of epithelium and maintains barrier function)

Physiological (factors that maintain corneal hydration)

- Endothelial pump**
- Barrier function of limiting layers**
- Stromal swelling pressure**
- Normal IOP**
- Evaporation from corneal surface

Corneal Metabolism

- Mainly **aerobic glycolysis**;
- Can function anaerobically only for 6-7 hours;
- Oxygen mainly derived from tear film
- Hypoxic corneal edema is due to accumulation of **lactate**

Nerve Supply

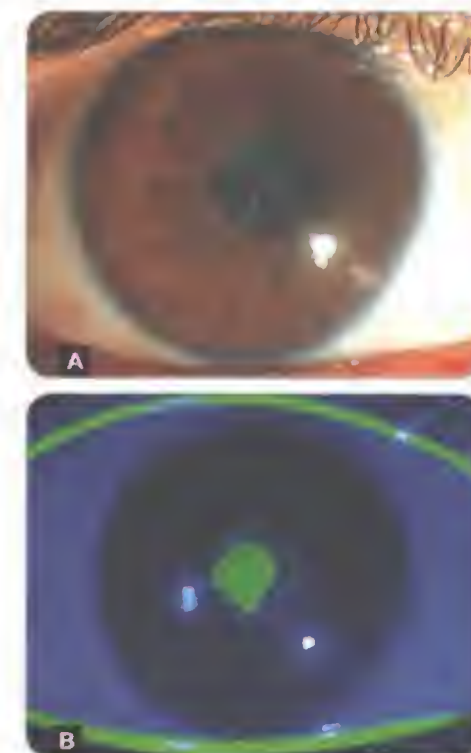
- Derived from the **long and short ciliary nerves**, branches of the **ophthalmic division of trigeminal nerve (CN V)**.

Blood Supply

- Cornea is **avascular**; but the limbus is supplied by anterior conjunctival branches of the **anterior ciliary arteries**.

Corneal Stains

- Fluorescein**: stains **corneal stroma**; used:
 - to detect **abrasions/epithelial defects**;
 - to detect **tear film breakup time** and
 - to detect aqueous humor leak in **Siedel's test**
- Rose Bengal**: Stains **devitalized epithelial cells** (lacking mucin); used in **diagnosing dry eyes**.



Figs 17.18A and B: Corneal abrasion. A. Normal view; B. Fluorescein staining

Pigment Deposition in Cornea

- All are **best seen by Slit Lamp Biomicroscopic Examination**.

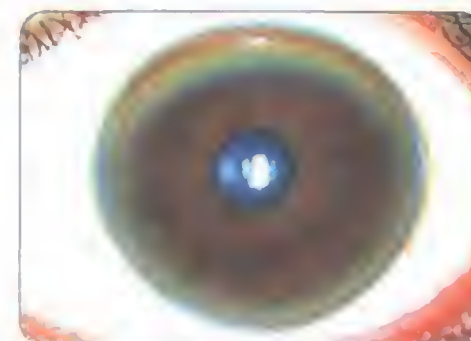


Fig. 17.19: K-F ring in Wilson's disease

Iron in epithelium (best seen with cobalt blue light)

- **Fleischer's ring** Keratoconus (at base of cone)
- **Stocker's line** Pterygium (at advancing edge)
- **Ferry's line** Filtering bleb (at edge)
- **Hudson-Stahli line** Old opacity

Iron in endothelium (best seen with cobalt blue light)

Copper in Descemet's membrane

- **Kayser-Fleischer's ring** Wilson's disease; Kayser-Fleischer-Copper = KFC! - earliest best seen by gonioscopy)

Melanin on endothelium

- **Krukenberg's spindle** Pigment dispersion syndrome

Causes of Reduced Corneal Sensation

- **Herpes simplex** and **zoster (viral)** keratitis
- **Leprosy**

CORNEAL CLINICAL CONDITIONS

Difference Between Bacterial and Fungal Keratitis

	Bacterial keratitis	Fungal keratitis (keratomycosis)
• Predisposing factors	Trauma by injury, foreign body, entropion, trichiasis, contact lens use; chronic dacryocystitis; underlying corneal disease (bullous keratopathy)	Trauma by vegetative/plant matter ; Indiscriminate use of topical steroids
• Etiology	Staphylococcus aureus , Streptococcus pneumoniae and Staphylococcus epidermidis ; Less common organisms include <i>Corynebacterium</i> species, <i>Propionibacterium acnes</i> , <i>Bacillus</i> species and <i>Neisseria gonorrhoeae</i>	Apergillus (MC in India); <i>Fusarium</i> ; <i>Candida</i>
• Symptoms	Acute pain, redness, watering, decreased vision, photophobia	Same symptoms but less severe
• Signs	Blepharospasm, lid edema, ciliary congestion	More signs Blepharospasm, lid edema, ciliary congestion
• Ulcer appearance	Wet looking grayish white ulcer with relatively distinct margins , hypopyon may be present (usually sterile)	Dry looking yellowish white lesion with feathery edges , satellite lesions seen, dense immobile hypopyon present which may NOT be sterile (since fungi can penetrate intact Descemet's membrane) Perforation and vascularisation are rare
• Treatment	Antibiotic eye drops and ointment Atropine/cycloplegics (to relieve ciliary spasm, prevent posterior synechiae formation) Antiglaucoma drugs	Antifungal eye drops and ointment (natamycin , Itraconazole) Silver sulfadiazine had been used earlier Atropine/cycloplegics Antiglaucoma drugs

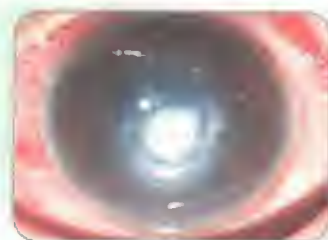


Fig. 17.20: Bacterial ulcer—staphylococcal

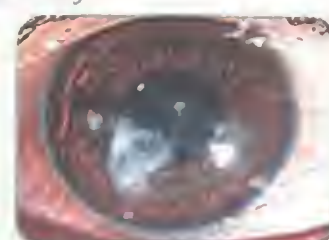


Fig. 17.21: Fungal ulcer with satellite lesions—filamentary

- **Diabetes Mellitus**
- **Riley day syndrome**
- **Section of trigeminal nerve**

Prominent Corneal Nerves Seen in

- **MEN 2b** (medullary thyroid Ca, pheochromocytoma, mucosal neuromas, marfanoid habitus), **Ichthyosis**, **Leprosy**, **Acanthamoeba keratitis**, **Neurofibromatosis**, (**MILAN**); **Refsum's disease**, **Keratoconus**, **Fuchs' corneal dystrophy**, **Congenital glaucoma**, **Corneal edema**, **Riley Day syndrome**.

Organisms Penetrating Intact Corneal Epithelium

- **Neisseria** (meningitis and gonorrhoea)
- **Corynebacterium diphtheriae**
- **Listeria**, **Shigella**
- **Haemophilus influenzae**

EXTRA EDGE

- Steroids are **contraindicated in both bacterial and fungal corneal ulcers**.
- If **contact lens user** develops keratitis, immediately **start antibiotic drops** and **discontinue the contact lenses**.
- For overwear syndrome, avoid wearing contact lenses for 48–72 hours.
- **Pythium insidiosum** keratitis is common in **Thailand** and now has been reported in India also; closely **mimics fungal keratitis** BUT **refractory** to medical treatment and often **penetrating keratoplasty** maybe required!

Few Corneal Terminologies

- Opacities may be graded from **least dense to most dense** as **Nebula < Macula < Leucoma** (remember 'leuco' - totally white = most dense; "NML = National Medical Library").
- A **central/paracentral leucoma on the cornea** is **much better** for visual prognosis since it causes less light scattering rather than a similar nebular/macular opacity.
- An ectatic cicatrix with incarceration of the iris is called **anterior staphyloma**.
- Corneal vascularization is called 'pannus'; **riboflavin (B2) deficiency** causes **pannus**.

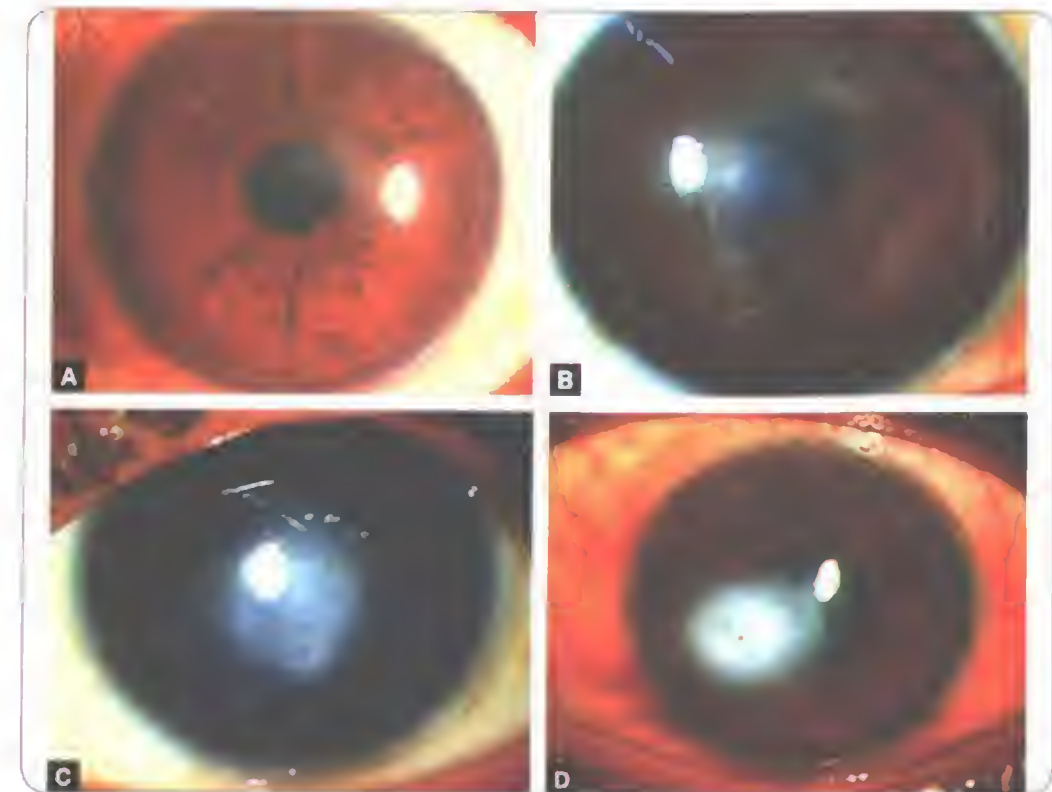


Fig. 17.22A to D: Grades of opacity. A. Nebular corneal opacity; B. Macular corneal opacity; C. Leukomatous corneal opacity; D. Adherent leukoma

Features of Certain Bacterial Corneal Ulcers

- **Ulcer serpens: Streptococcus pneumoniae** (pneumococcus)
- **Hypopyan corneal ulcer**: term specifically reserved for **Streptococcus pneumoniae** (pneumococcus)
- **Pseudomonas**: **greenish exudates**, affects **contact lens wearers**, rapidly **progressive**, cornea can **perforate within 48 hours**.
- **Staphylococcus aureus**: **grayish white dense opaque stromal ulcer** surrounded by relatively clear cornea

Herpes Simplex Keratitis

Epithelial keratitis

- Caused by **actively replicating virus** on corneal surface
- **Reduced** corneal sensation
- **Dendritic ulcer**: dichotomously branching lesion with **terminal bulbs**; borders staining with Rose Bengal, epithelial defect stains with fluorescein
- **Geographic ulcer (amaeoid ulcer)**

Chitral

Epithelial keratitis

- Marginal keratitis
- **Metaherptic/traphic ulcer**; NOT a/w live virus and is due to inability of epithelium to heal
- **Resolves spontaneously** in 50% cases
- **Topical Antivirals** are mainstay of treatment

Stromal/endothelial keratitis

- **Immune mediated response** to non-replicating virus particles
- **Immune stromal keratitis (Disciform keratitis; a/w Wessle's immune ring)**
- **Endotheliitis**
- **Necrotising keratitis (uncamman)**
- **Keratauveitis (a/w secondary glaucoma)**
- **Topical steroids are mainstay** (esp. for stromal keratouveitis) with topical and oral antiviral cover is necessary; topical steroids may need slow tapering over months.

Herpes Zoster Ophthalmicus (Shingles)

- Caused by **Varicella zoster virus**.
- **Hutchinson sign**: Involvement of **external nasal nerve** which supplies the side of the tip and side of the root of the nose; correlates significantly with subsequent development of ocular inflammation since it is the **terminal branch of the nasociliary nerve**.
- Age: MC in 6-7 decade.
- **AIDS**: HZO in children or young adults; **suspect AIDS or immunodeficiency**.
- Ocular Acute disease
 - Acute **epithelial keratitis**: **pseudodendrites** with **tapered ends** (simplex has dendrites with terminal bulbs)
 - **Stromal keratitis**; **endotheliitis**; mucus plaque keratopathy; interstitial keratitis; neurotrophic keratopathy; exposure keratopathy
 - Can be a/w **anterior uveitis (sectoral iris atrophy)**;
- Treatment: Stromal keratitis and uveitis will require topical steroids with oral acyclovir cover.
- **Postherpetic neuralgia**: Develops in **75% patients** over 70 years of age; reduces with time; NSAIDS are ineffective; topical **capsaicin cream**; **amitryptiline**; **carbamazepine**.



Fig. 17.23: Dendritic ulcer in HSV keratitis



Fig. 17.24: Herpes zoster ophthalmicus—Hutchinson's sign

Acanthamoeba Keratitis

Etiopathogenesis

- **Free living protozoa** (no human host required for life cycle completion) with **active trophozoite** and **dormant cystic form**.
- **Present in soil, water** (highly resistant to chlorinated water in **swimming pools** – so don't swim with your contacts on!)
- Affects **extended wear soft contact lens wearers**, also affects those who use homemade saline for cleaning lenses, precipitated by **corneal trauma**.

Clinically

- **Severe pain** (disproportionate to lesion); **corneal ring infiltrates**; **radial keratoneuritis**.
- Diagnosed by staining scrapings with **Giemsa**, **Calcofluor white** / **acridine orange**.
- Culture on **non-nutrient agar with overlay of E.coll.**
- Cyst can be demonstrated in vivo in cornea with **confocal corneal microscopy**.



Fig. 17.25: Ring infiltrates in acanthamoeba keratitis

Treatment

- **PIMB** eyedrops (polyhexamethylene biguanide).
- **Propamidine** isethionate, Chlorhexidine, imidazoles (miconazole), neomycin eyedrops.

Keratoconus

Early Signs

- **Keratometry/Placido's disc**: Irregular rings; **Scissor reflex on retinoscopy**; Direct ophthalmoscopy: **Oil drop sign**; **Vogt's striae** (Vertical lines); **Prominent corneal nerves**.

Late Signs

- **Fleischer's ring**: Iron deposition in epithelium at base of cone.
- **Munson's sign**: bulging of lower lid when patient looks down.
- **Rizzuti sign**: corneal reflection on the nasal limbus when light is thrown from the temporal limbus.
- **Acute hydrops**: sudden corneal edema due to rupture of Descemet's membrane.
- Corneal scarring.

Etiology

- Chromosomal disorders (Down's syndrome); Connective tissue disorders (Marfan's syndrome); Cutaneous disorders (atopic dermatitis); Contact lens wear; Congenital eye anomalies (aniridia, Leber's amaurosis). 5 Cs

Corneal Stromal Dystrophies

Feature	Granular	Lattice	Macular
Inheritance	AD	AD	AR
Diminished vision	By 4th or 5th decade	By 2 nd or 3 rd decade	1 st or 2 nd decade
Corneal Erosions	Uncommon	Frequent	Uncommon
Opacities	Discrete sharp borders Intervening stroma clear early but becomes hazy Limbal zone clear	Early Refractile tiny criss cross lines and dots Subepithelial spots Diffuse central haze	Indistinct margins Hazy intervening stroma Extends to limbus Endothelium affected
Corneal thickness	Normal	Normal	Thinned
Material accumulated	<u>Hyaline</u>	<u>Amyloid</u>	<u>Mucopolysaccharides</u>
Stains	<u>Masson's trichrome</u>	<u>Congo red</u>	<u>Alcin blue</u>
Distinguishing clinical features	Clear limbal zone	Lattice lines	Opacities reach limbus Cornea thinned MOST SEVERE

Mnemonic for material accumulated and stains in corneal dystrophies (see bold and underlined letters in table

above): "Marilyn Monroe Always Gets Her Men In L.A. City"

Treatment of Keratoconus

- **Hard (RGP)** contact lenses
- Penetrating keratoplasty (has **excellent success**)
- Newer treatments:
 - **Rose K** contact lens
 - **INTACS** (INTrACorneal ring Segments)
 - DALK (Deep Anterior Lamellar Keratoplasty)
 - C3R (Corneal Collagen Cross linking with Riboflavin eye drops)

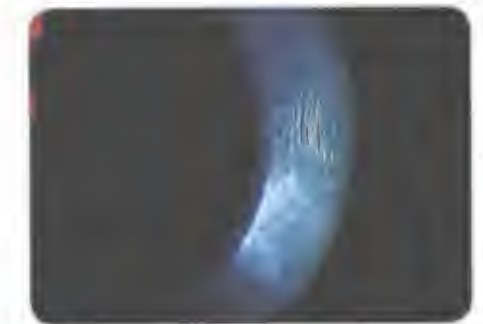


Fig. 17.26: Vogt's striae in keratoconus

EXTRA EDGE

- **Corneal collagen cross linking (also called C3R, CCL, CxL)** is a new treatment for **keratoconus** to increase the mechanical and chemical stability of corneal tissue. Apply **Riboflavin (vitamin B2) eyedrops** (photo-educator) and expose the cornea to **UV-A light** for a fixed duration (about 1 hour).

More about corneal dystrophies

- Corneal dystrophies are usually described as **hereditary, bilateral, progressive, and not a/w systemic or local disease**
- MC Anterior Corneal Dystrophy = **Epithelial Basement Membrane Dystrophy** (A.k.a map dot fingerprint dystrophy)
- MC Stromal Corneal Dystrophy = **Lattice dystrophy** (type 1 MC) - Macular dystrophy is **LEAST** common
- MC Posterior/Endothelial Corneal Dystrophy = **Fuch's endothelial dystrophy**
- Dystrophies affecting Bowman's membrane: **Reis Buckler's; Thiel behnke and Graysan wilbrandt.**



Fig. 17.27: Band-shaped keratopathy

Trophic vs paralytic

- Reduced corneal sensation (trigeminal 5th nerve affection) causes = **neurotrophic** keratitis
- Facial (7th) nerve **paralysis** causes = **neuroparalytic** keratitis

Photophthalmia/Photokeratitis

- Etiology:** Caused by **exposure to UV rays**. Examples are:
 - Welding arc keratitis** — Viewing welding arc with naked eyes; **Snow Blindness** — Exposure to UV rays reflected from snow surfaces.
- Clinically:** **6–12 hrs after exposure (latent period), bilateral severe eye pain, photophobia, and blepharospasm.**
- Self-limited condition with complete resolution.

Interstitial Keratitis

- MC in **first or second decades**;
- Ghost vessels in cornea**
- Etiology:** **Congenital syphilis** (bilateral); **Cogan syndrome** (bilateral, vertigo, tinnitus, hearing loss, negative syphilis serology), **polyarteritis nodosa**.

Peripheral Ulcerative Keratitis (PUK)

- MC a/w **rheumatoid arthritis**.
- Autoimmune** complex deposition in peripheral cornea → inflammation → circumferential spread.
- End stage disease results in '**contact lens cornea**'.
- Unlike Mooren's ulcer, process **may extend to involve the sclera**.

WHO Grading of Xerophthalmia (Vitamin A Deficiency)

- X1** = Conjunctival xerosis (X1A) with Bitot spot (X1B)
- X2** = Corneal xerosis

- X3** = Corneal ulceration (**keratomalacia**) < one third (X3A); > one third (X3B; Keratomalacia – **sterile corneal melting by colliquative necrosis** (absence of inflammation)).
- XN** = **Night blindness** (**earliest manifestation**)
- XS** = Corneal scar
- XF** = Xerophthalmic fundus (**Uyemura's fundus**)
- Above
- X₁** = Type Primary signs
- Below X₁ and before XN type Secondary signs

Primary signs	Secondary signs
X ₁	XN
X ₂	XS
X ₃	XF

Treatment Schedule for Keratomalacia

- Vitamin A in **3 doses**: First dose **AT diagnosis**; second **after 24 hours** and the third **after 2 weeks**.
- Oral vitamin A oil based preparations are preferred**; if child has vomiting/diarrhea, then IM injection of water miscible vitamin A (retinyl palmitate) may be given at half dosages.

Age	Preparation (orally)	Dose
< 6 months	Retinyl palmitate	50,000 IU
6–12 months or weight < 8 kg	Retinyl palmitate	1,00,000 IU
> 12 months and weight > 8 kg	Retinyl palmitate	2,00,000 IU

EXTRA EDGE

- Bitot's spots** are triangular white spots resembling 'dried foam' and are not wet by tears; occur due to gas production by **Corynebacterium xerosis** present in the horny epithelium.

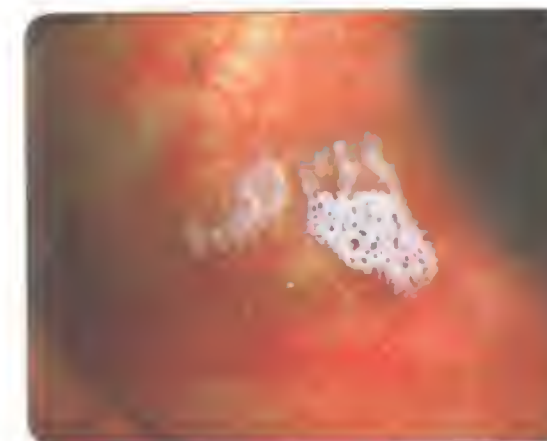


Fig. 17.28: Bitot's spot

DRY EYES

Precorneal Tear Film

- Outer **Lipid** layer secreted by **MEibomian** glands
- Middle **Aqueous** layer secreted by **Lacrimal** and accessory lacrimal glands.
- Inner **Mucin** layer secreted by conjunctival **Goblet** cells (Love **ME** Always My Girl!).

Types of Dry Eyes

Aqueous deficiency (Evaporative dry eye)

- Due to **lacrimal gland disease** by:
 - Sjögren's syndrome** (Keratoconjunctivitis sicca: Triad of **dry eyes, dry mouth and rheumatoid arthritis**) and other conditions affecting lacrimal gland (pemphigoid, radiation etc.).

Lipid Deficiency Dry Eye

- Due to **meibomian gland disease** from:
 - Blepharitis, Meibomitis, Anhidrotic ectodermal dysplasia (congenital absence of meibomian glands).

Mucin Deficiency

- Due to **goblet cells disease** by:
 - Conjunctival scarring (alkali burns, trachoma, pemphigoid), hypovitaminosis A, Drug induced.

Tests for Dry Eyes

Schirmer Test

- For measurement of **tear production, mainly the aqueous phase of tear** Maybe done:
 - With topical anesthesia = basal tear secretion: Schirmer I)
 - Without topical anesthesia (reflex tear secretion): Schirmer II.
- Less than 5 mm wetting of the tear strip at 5 min** is used for confirmation of dry eye.

Tear Film Break Up Time (TBUT)

- Fluorescein sodium** dye is applied to the eye and observed under cobalt blue light of the slit lamp.
- TBUT is the **time interval measured between the last blink and the appearance of the first dry spot**.
- TBUT is widely used for determining the stability of precorneal tear film and **identifying patients with evaporative dry eye**.
- A TBUT of **more than 10 s** is considered a normal value.

Rose Bengal Staining

- To **detecting devitalized epithelial cells** and grading the six quadrants.

Fuchs' Endothelial Dystrophy

- Glare and blurred vision** worse on **awakening in morning**; may progress to pain due to **ruptured bullae**; symptoms **commonly after 50 years**.
- Autosomal dominant, bilateral**; corneal guttae.
- Topical **hypertonic saline drops, hairdryer** in mornings to dehydrate the cornea and therapeutic **soft contact lenses**.
- Definitive treatment** is keratoplasty: **DSEK** (Descemet's stripping endothelial keratoplasty); **penetrating keratoplasty** needed if anterior stromal scarring is present

EXTRA EDGE

- Other endothelial dystrophies are **Posterior polymorphous dystrophy** and **congenital hereditary endothelial dystrophy**.

Vortex Keratopathy

- Vortex Keratopathy or Cornea Verticillata** consists of symmetric, bilateral, **whorl-like pattern** of powdery, white/yellow corneal **epithelial** deposits; **not of much visual significance**.
- Caused by: **Fahry's disease**; drugs (**Amiodarone, Chloroquine, Amodiaquine, Meperidine, Indomethacin, Chlorpromazine, Tamoxifen**).

Band Keratopathy

- Band keratopathy** — deposition of **calcium** in **bowman's membrane, epithelial basement membrane and anterior stroma**.
- Ocular causes: **Chronic anterior uveitis** (esp. in children with **JRA**); **phthisis bulbi, silicone oil in anterior chamber, chronic corneal edema, severe chronic keratitis**.
- Others: Age related; metastatic calcification (increased serum calcium and phosphorus, chronic renal failure, hyperuricemia); **sarcoidosis**, familial and ichthyosis.
- Treatment: **chelation with EDTA**.



Fig. 17.29: Schirmer's test

EXTRA EDGE

Recent advances

Other methods for dry eye evaluation are:

- **High tear osmolarity**
- **Conjunctival impression cytology** (to look for number of goblet cells, morphology of epithelial cells and nucleocytoplasmic ratio)
- **Lipview: Tear film interferometry.**
- **Delphi panel** report gives the severity scale for dry eye.

CORNEAL TRANSPLANTATION

Eye Banking

- Donor corneas are harvested from cadaveric donors **within 6 hours of death** (upto 12 hours in cold countries).
 - **Short term** preservation (maximum upto 96 hours): **Moist chamber method, M-K media** (McCarey Kaufman)
 - **Intermediate term** (upto 30 days): **organ culture** methods.
 - **Long term** (upto 1 year): **cryopreservation.**

Types of Keratoplasty

- **Optical** keratoplasty: To provide a **clear visual axis** and restore vision.
- **Therapeutic** keratoplasty: To **remove infected/sloughing cornea** involving whole cornea.
- **Tectonic** keratoplasty: To **preserve corneal integrity** in eyes with sever structural changes such as stromal thinning or descemetoceles.

Penetrating Keratoplasty

- Penetrating keratoplasty (PK) is **full-thickness** corneal transplantation.

- MC indication for PK In **India**, is **corneal scar** (**leucoma**) usually due to healed infections keratitis. In the west, It is **corneal edema** (esp. **bullous keratopathy** pseudophakic or aphakic).
- **Specular microscopy** is used to determine **endothelial cell count**. Methods used are: **Frame method** (**variable frame** and **fixed frame**); **Comparison method**; **Cornu method** and **Centre method**.
- Donor cornea is **NOT** used in the following circumstances:
 - Death due to unknown cause.
 - Infections diseases of CNS: C-J Disease, Subacute Sclerosing PanEncephalitis, Progressive Multifocal Leukoencephalopathy.
 - Infections, systemic: AIDS, viral hepatitis, syphilis, septicemia.
 - Leukemia and lymphoma
 - Intrinsic eye disease (malignancy, inflammation) or previous intraocular surgery.
- **Urrets Zavalia syndrome: Fixed dilated pupil** as an early complication of PK.

Lamellar Keratoplasty

Definition: **Partial thickness keratoplasty** to avoid the complications of PK (astigmatism, endothelial rejection) — only the diseased portion of the cornea is replaced.

Anterior Lamellar Keratoplasty	Posterior Lamellar Keratoplasty OR Endothelial Keratoplasty
(for anterior corneal pathologies) Indications: Keratoconus (MC) Anterior stromal scars and pathologies	(for posterior corneal pathology) Indications Corneal endothelial decompensation due to any of the below: Congenital hereditary endothelial dystrophy, Fuch's endothelial dystrophy, Bullous keratopathy, ICE syndrome, Epithelial or fibrous down growth
Types	Types
DALK: Deep Anterior lamellar Keratoplasty (outermost 250 microns are replaced); Total cornea stroma upto Descemet's membrane is removed In manual DALK, Anwar's big bubble technique is used	DSEK: Descemet's stripping endothelial keratoplasty; Endothelium and Descemet's membrane are stripped and posterior corneal lamella is replaced DSAEK: (Automated DSEK); - reported endothelial cell loss is 30-40%

Keratoprosthesis

- Artificial corneal implants designed to replace the cornea in patient unsuitable for penetrating keratoplasty/ repeated keratoplasty failures.
- Central optical cylinder is made of **PMMA** (polymethyl methacrylate) with a surrounding fixation device made of various materials - **osteo-odonto**-keratoprosthesis (tooth and bone); **chondro**-keratoprosthesis (cartilage); **uncylich**-keratoprosthesis (nail).

Stem-cell Grafting

- Limbal epithelial stem cells reside in the **limbal palisades of Vogt** at the highly vascular limbal rim.
- These cells can get damaged in chemical burns and cleansing disorders.
- Autologous stem cell transplantation (from the same or other eye) has proven effective for reconstructing damaged ocular surfaces.
- **ABC G2** is a **universal marker of stem cells** and also a **limbal epithelial stem cell marker**.

Corneal Allograft Rejection

- **Endothelial rejection** is **MC** and most severe.
- **Type IV** hypersensitivity reaction.
- **Epithelial** rejection: Elevated abnormal epithelium
- **Stromal** rejection: Subepithelial infiltrates on donor cornea (**Kraemer spots**)
- **Endothelial** rejection: Linear pattern of keratic precipitates (**Khodadoust line**).

Contraindications for Corneal Transplantation (as per NPCB)

(I) Conditions with potential risk of transmission of local or systemic communicable from donor to recipient

Absolute Contraindications

- Death of unknown cause
- Death with neurologic disease of unestablished diagnosis*
- Active meningitis or encephalitis*
- Encephalopathy of unknown origin or progressive encephalopathy*
- Active septicemia* (bacteremia, fungemia, viremia, parasitemia)
- Active viral hepatitis*
- Creutzfeldt-Jakob disease*
- Rabies*
- Active military tuberculosis or tubercular meningitis*

- Hepatitis B surface antigen positive donors*
- HTLV-I or HTLV-II infection*
- Hepatitis C Seropositive donors*
- HIV seropositive donors*
- HIV or high risk for HIV corneas from: persons meeting any of the following criteria should not be offered for transplantation

Others Contraindications

- Subacute sclerosing panencephalitis
- Progressive multifocal leukoencephalopathy
- Congenital rubella
- Reye's Syndrome
- Patients on ventilator for > 72 hrs
- Active ocular or intraocular inflammation conjunctivitis, scleritis, iritis, uveitis, vitritis, choroiditis and retinitis (at the time of death).

(II) Conditions with potential risk of transmission of non-communicable disease from donor to recipient.

- Death due to cyanide poisoning
- Intrinsic eye disease
- Retinoblastoma
- Malignant tumors of the anterior ocular segment or known adenocarcinoma in the eye of primary or metastatic origin.
- Leukemias (absolute CI)
- Active disseminated lymphomas (absolute CI)

(III) Conditions that will affect graft outcome.

- Congenital or acquired disorders of the eye that would preclude a successful outcome for the intended use e.g., a central donor corneal scar for an intended penetrating keratoplasty preserve of keratoconus and keratoglobus. Corneas which have undergone refractive surgical procedures etc.
- Patients on ventilator for >72 hrs.

DISEASES OF SCLERA

Sclera

- Sclera covers posterior five-sixths of the eye; It has two large openings, the anterior (corneal window) and the posterior (for optic nerve).
- Structures piercing the sclera are: 4 vortex veins (4 mm behind equator); long and short ciliary nerves; long and short ciliary vessels; anterior ciliary nerves and vessels.
- Sclera is **thickest posteriorly surrounding the optic nerve** (1 mm) and is **thinnest just posterior to the insertion of the recti muscles** (0.1 mm)

Episcleritis

- A **benign recurrent inflammation of the episclera** involving the overlying Tenon's capsule but NOT the underlying sclera.
- Typically affects **young adults**; a/w **mild pain/irritation**; localized redness; nodule maybe present in Nodular episcleritis; **Resolves spontaneously** in 2-3 weeks; **recurrences are common**.
- Treatment: Topical weak corticosteroid drops; cold compress; systemic NSAIDs.

Scleritis

- A **chronic inflammation of the sclera** which is **much serious** and if untreated may cause **visual impairment and loss of the eye also**.
- Usually **bilateral** and more common in **women**.
- **MC associated disease is rheumatoid arthritis**; a/w connective tissue disorders in 50% of cases.
- Symptoms: **Intense deep-seated pain**, which radiates to forehead, **Intense redness**.
- **Scleromalacia perforans**: anterior necrotising scleritis without inflammation (painless); typically occurs in **female patients with longstanding rheumatoid arthritis**.
- Treatment: Systemic **NSAID's** (indomethacin); Oral/Topical/Periocular/systemic **steroids**; Cytotoxic agents, Immune modulators.; **Subconjunctival steroids are contraindicated** since they may cause scleral thinning and perforation.

Posterior Scleritis

- NOT a/w specific systemic diseases;
- Inward extension (towards choroid) of the inflammatory process gives rise to '**uveal effusion syndrome**'—choroidal effusion, exudative retina detachment etc.;
- **Proptosis, reduced motility and visual loss**.
- B-scan shows "**T-sign**" (fluid in Tenon's space).

Staphyloma

- **Staphyloma** refers to a **localized bulging (ectasia)** of weak and thin outer tunic of the eyeball (cornea or sclera) lined by uveal tissue, which shines through the thinned out fibrous scar coat.

Staphyloma	Definition
Anterior	A protrusion of the cornea with incarceration of the iris

Contd..

Staphyloma	Definition
Intercalary	Ectasia of the sclera with incarceration of the root of the iris
Ciliary	Ectasia of the sclera with incarceration of the ciliary body
Equatorial	Ectasia of the sclera with incarceration of the choroids
Posterior	Bulge of the weak sclera lined by choroid behind the equator, seen in high myopia

Scleral Discoloration

- **Bluish grey or black sclera**: **Alkaptonuria**
- **Hemochromatosis**: **rusty brown** sclera.
- **Blue sclera**: due to visibility of the underlying uveal pigment through the thinned sclera; normally in **babies**; **Osteogenesis imperfecta**; **Marfan's syndrome**; **Ehler Danlos syndrome**; **pseudoxanthoma elasticum**; **buphthalmos**; **high myopia**; **healed scleritis**; **Marshall Smith syndrome**, **Russell Silver syndrome**, **Hallermann Steriff Francois syndrome**.

LENS BASICS

Lens Anatomy

- Lens is placed between the iris and vitreous in a saucer shaped depression — **patellar fossa**; the potential retrolental space is called **Berger's space**.
- **Anterior Lens epithelium** — Single layer of **cuboidal epithelium**; in the equator it is **columnar and these cells actively divide to form new lens fibres throughout life**. There is **NO posterior lens epithelium** as these cells are used up in filling the central cavity of the lens vesicle during development of the lens.
- **Lens capsule** — **Thinnest at the posterior pole** and thickest in the pre-equatorial region. The **oldest portion of the capsule is the most superficial layer**. **Lens capsule is the thickest basement membrane in the body**.
- **Lens nucleus** — The **oldest portion of the lens is the deepest central nucleus**. Cortex consists of youngest fibres lying superficially.
- **Refractive index** of nucleus (1.406) > cortex (1.386).
- **Suspensory ligament** — of Zinn, or zonules connect ciliary body to lens and enable ciliary muscle to act on lens.

Lens Physiology and Biochemistry

- Lens is **avascular** and has **NO nerve supply**.

- Nutrition is derived from **aqueous, vitreous**, perilimbal capillaries and air (oxygen).
- Lens is composed of 64% water.
- **The protein concentration in lens is the highest among body tissues** — the main proteins are **crystallins** — **alpha, beta (max — 55%) and gamma crystallins**.
- **High molecular wt proteins** in human **cataractous lens** are **HM3 and HM4**.
- **Lens cortex is the most metabolically active region**. Metabolism is mainly **anaerobic glycolysis** — embeds Meierhof pathway (85%) and 15% by pentose phosphate pathway.
- **Anti-oxidant protection** (against reactive oxygen species) to the lens is by **glutathione peroxidase, catalase, ascorbic acid (Vitamin c), alpha tocopherol (vitamin E)** and **beta-carotene** (precursor of vitamin A).

- **Glutathione** normally functions to maintain ascorbate, and alpha-tocopherol in **reduced states**.
- **Yellowing/browning of lens nucleus** with age is due to accumulation of photo-oxidation pigment **urochrome**.
- **MIP-26** (Major Intrinsic Protein) may play a role in **enhancing lens transparency**.
- **Lens is the MOST radiosensitive** structure in the eye; **sclera is LEAST radiosensitive**.
- Mutations in **CRYAA gene** and **PITX3 gene** cause **AD congenital cataract**.
- Mechanism of **cortical cataract** formation: Decreased levels of total proteins, amino acids and potassium a/w increase of sodium and marked hydration of lens followed by coagulation of proteins.
- Mechanism of **nuclear cataract** formation: Increase in **water insoluble proteins**.

CATARACTS

Type of cataract	Significant features
Congenital cataract	
Blue dot cataract (cataracta caerulea)	NO significant visual symptoms, non progressive
Zonular (lamellar) cataract	MC type of congenital cataract ; A/W malnutrition, vitamin D deficiency, Hypocalcemia . Riders are seen
Coronary cataract	Club shaped opacities, non progressive, vision NOT affected
Posterior polar	Persistence of the posterior part of the vascular sheath of the lens; High risk of posterior capsule rupture during surgery; NO hydrodissection during surgery.
Rubella cataract	Congenital pearly nuclear cataract with necrosis of lens nucleus ; also a/w salt n pepper retinopathy ; microphthalmos , microcephaly , mental retardation , deafness , dental anomalies , PDA
Infective	Other Intrauterine infections a/w cataract are toxoplasmtic , CMV , herpes simplex and varicello
Skeletal syndrome	Hallerman- Steriff syndrome .: Membranous cataract with spontaneous absorption of lenticular material ; Other features (progeria , frontal baldness , small beaked nose , micrognathia , hypodontia) Nonce Horon syndrome : Dense cataracts; female carriers may show Y suture opacities ; Other features (supernumerary incisors , prominent ears , anteverted pinnae , short metacarpals)
Chromosomal abnormalities	Down's syndrome (cataract occurs in 75% patients in late childhood), Patau's (trisomy13) and Edward's (trisomy 18) also a/w cataract
Anterior Lenticonus	ALports syn. (familial hemorrhagic nephritis and sensorineural deafness) ; oil globule reflex on direct ophthalmoscopy
Posterior lenticonus	Lowe's (oculocerebrorenal) syndrome
Senile cataract (MC cause of cataract)	
Posterior subcapsular cataract	Most visually handicapping even in the early stages owing to the position of the opacity near the nodal point of the eye ; more blurring in bright sunlight and headlights of oncoming cars

Contd

Contd...

Type of cataract	Significant features
Nuclear cataract	"Second sight" due to induced myopia (person who was using glasses to read earlier will be able to read better without glasses !!)
Cortical cataract	'Spokes' like opacities, causes glare due to light scattering; can cause colored haloes and monocular diplopia or polyopia ; incipient cataract is a stage of cortical cataract formation
Morgagnian cataract	A hypermaturation cataract in which liquefaction of the cortex has allowed the nucleus to sink inferiorly
Physical agents	
Radiation cataract	Posterior subcapsular cataract ; can occur with x-rays, gamma rays, cosmic rays, neutrons, UV rays, ionizing radiation, nonionising rays (infrared cataract – glassblowers cataract and furnace workers/heat cataract – a/w true exfoliation of lens capsule)
Traumatic cataract	Rosette cataract, Vossius ring (pigments on anterior lens capsule due to constricted pupil striking lens during blunt trauma)
Electric cataract	Anterior subcapsular cataract ; if shock is to one side, cataract develops on that side
Toxic cataract	
Corticosteroid induced cataract	Posterior subcapsular cataract - MC with oral steroids (Note: glaucoma MC with topical steroids)
Drug induced (others)	Anticholinesterases (DFP, echothiophate), miotics, chlorpromazine (anterior capsular golden deposits), busulfan, chloroquine, amiodarone, gold, iron
Dermatological diseases	
Syndermatotic cataract	Cataract a/w skin diseases like atopic dermatitis (MC) , psoriasis, keratosis follicularis, ectodermal dysplasia, ichthyosis, Rothmund's syndrome, Werner's syndrome, incontinentia pigmenti, Cockayne's syndrome
Shield cataract	Atopic dermatitis (anterior subcapsular plaque)
Secondary (complicated) cataract	
Etiology	Due to any disease process in eye; seen are palychromatic lustre, Bread crumb appearance
Causes of complicated cataract	Chronic anterior uveitis (MC cause); acute congestive glaucoma (anterior subcapsular opacities are pathognomonic – glaucoma flecken), high myopia (early onset of nuclear sclerosis), hereditary fundus dystrophies (RP, Leber's congenital amaurosis, gyrate atrophy, Stickler syndrome)
Systemic diseases	
Oil drop cataract	Galactosemia (due to galactitol accumulation in lens)
Microphakia	Lowe's syndrome : oculocerebrorenal syndrome, lens is small thin and disc-like - microphakia ; X linked (Note: Microspherophakia is different – seen in Weil Marchesani syndrome – see ectopia lentis below)
Diabetic cataract	In diabetes mellitus, in the lens glucose is converted to sorbitol by aldose reductase & sorbitol accumulates in lens causing osmotic overhydration of lens – diabetic cataract (snowflake cataract). Aldose reductase inhibitors are being studied to prevent diabetic cataract; Early diabetic cataract maybe reversible - "reversible cataract" .
Sunflower cataract	Wilson's disease; Chalcastis (excess copper accumulation in lens); K-F ring – copper in Descemet's membrane of cornea
Christmas tree cataract	Myotonic dystrophy ; Other features: muscle wasting, premature baldness, gonadal atrophy, cardiac conduction defects, mental retardation
Others metabolic cataracts	Hypoparathyroidism, pseudohypoparathyroidism, Fabry's disease, mannosidosis, hypoglycemia, hyperglycemia

TYPES OF SENILE CATARACT

- Cortical or soft cataract (75–80%): The classical changes of hydration followed by coagulation of lens proteins occurs mainly in the cortex.
- Nuclear or hard cataract (20–25%): Slow progressive sclerosis of lens nucleus occurs.

Cortical (Soft Cataract)

Cupuliform

- It starts as a **wedge shaped** opacity in the periphery and gradually extends to the centre
- Symptoms:
 - Painless progressive loss of vision
 - Unilateral **diplopia/polyopia**
 - Coloured haloes** and Glare
- Stages and signs
 - Stage of lamellar separation
 - Stage of **incipient** cataract: **Wedge-shaped** opacities MC in **lower nasal** quadrant.
 - Immature stage
 - tumescient** cataract (swollen lens—can lead to secondary **acute angle closure** glaucoma)
 - Mature** cataract (PL vision, pearly white lens, fundal glow absent, iris shadow absent, fourth Purkinje image absent)
 - Hypermaturation stage (see box below)

Types of Hypermaturation cataract

- Hypermaturation **Morgagnian** cataract: Cortex liquifies and the nucleus sinks to the bottom within the lens capsule.
- Hypermaturation **Sclerotic** cataract: Shrunken nucleus due to loss of fluid from the lens.

Cupuliform Cataract (Posterior Cortical Cataract)

- Markedly diminished vision** since opacity is near the nodal point of the eye.
- Fourth Purkinje Image** is blurred.
- Patients see **better at dusk** (evenings).
- Yellowish white** opacity in posterior cortex is seen.

Nuclear (Hard) Cataract

- LOCS III: Lens Opacity Classification System** is used to grade the cataracts based on a standard set of photographs.

- Cataract brunescens** (brown cataract) and **Cataract nigra** (black cataract) are advanced types of nuclear cataract.
- Patients may complain that their reading/near vision has improved and they are able to read without glasses compared to earlier (**second sight!** - occurs due to index myopia, increased refractive index of cataractous lens nucleus).
- Vision maybe **hand movements** only; lens is **yellow or brown colored**; iris shadow usually present; **fundal glow** present; retinoscopy may show **myopia**.

CATARACT SURGERY

Anesthesia for Ocular Surgery: Local (Regional) Anesthesia

- Topical (surface) anesthesia**: topical instillation of **4% xylocaine or proparacaine**. Modern day phacoemulsification can be safely done under topical anesthesia with a cooperative patient and an experienced surgeon.
- Facial block**:
 - To **block the facial nerve**, which **supplies the orbicularis oculi** so that patient **does not squeeze the eyelids**. Blocking the facial nerve at its terminal branches **near the lateral angle of eye** (**Van Lint's method**); **superior branches** (**Atkinson block**) or proximal trunk **near the condylar process of mandible** (**O'Brien or Nadbath block**). **Additional retrobulbar block** is needed.
- Retrobulbar Block**:
 - This **anesthetizes the ciliary nerves, ciliary ganglion, third and sixth cranial nerves**, thus producing globe akinesia, anesthesia and analgesia. **Superior oblique muscle** is usually NOT paralyzed since the **fourth cranial nerve is outside the muscle cone**. **Complications** include **retrobulbar hemorrhage, globe perforation, optic nerve injury and extraocular muscle palsy**.
- Peribulbar Block**:
 - Fewer complications** and **avoids the need for a separate facial block**.

Preoperative Evaluation

- Slit lamp examination; Lacrimal syringing; Treat all infections (meibomitis, blepharitis etc.); Indirect ophthalmoscopy; IOP measurement

Retinal/Macular function tests:

If this is defective patients should be warned of a guarded visual prognosis.

- › Perception of light
- › Projection of rays
- › Two point discrimination test
- › Pupillary reaction
- › Maddox rod test
- › Color perception
- › Entoptic phenomenon
- › Laser interferometry
- › Potential visual acuity meter

Biometry

- **Biometry** is the process of *calculating the power of IOL* to be implanted.
- Most widely used formula is the Sanders-Retzlaff-Kraff (**SRK**) **formula**; If E is the emmetropic power for the eye in question, and A is a predetermined constant for each IOL, then

$$E = A - 2.5L - 0.9K$$
(L is the axial length of the eye and K is the average of keratometry readings).
- Other formulae:
 - › **Holladay** formula: for long eyeballs/high refractive errors

- › **SRK II** formula: adjusts for unusually long or short eyeballs
- › **Hoffer** formula, **SRK-T** formula

EXTRA EDGE

Recent advances

- **Immersion biometry** uses a water bath and is **more accurate** than direct contact biometry.
- **IOL Master** and **Lenstar** calculate *keratometry and axial length* by **non-contact method**.



Fig. 17.30: Rosette cataract

INTRAOCULAR LENSES

Non-foldable (Rigid) IOL	Foldable IOL	Multifocal IOLs
Made of PMMA (Polymethyl methacrylate) Maximum used in developing countries	Silicone IOL : lower rate of posterior capsule opacification (PCO) than PMMA IOLs; more likely to have anterior capsular contraction than acrylic IOLs. Acrylic IOLs Hydrophobic (water content < 1%): have much higher refractive index and hence <i>thinner</i> . Hydrophilic (water content 18-35%): higher incidence of PCO Hydrogel IOLs : similar to hydrophilic acrylic IOLs.	Allow clear vision for both distance and near. Helps in achieving freedom from spectacles

EXTRA EDGE

- IOL invented by Sir **Harold Ridley**.
- Father of **phacoemulsification** - **Charles Kelman**.
- **Blue blocking/Yellow colored IOLs**: have filters for blue light to prevent damage to retina by blue light.
- **Aspheric IOLs**: to minimize spherical aberrations.
- **Toric IOLs**: to correct preexisting corneal astigmatism.
- **Toric Multifocal IOLs**: multifocality with toricity.
- **Heparin coated IOLs**: useful in **uveitis patients**.
- Trypan blue is used for staining capsule during capsulorhexis

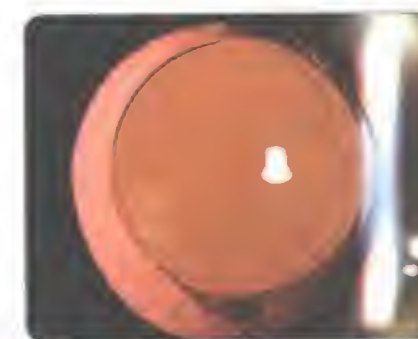
ICCE	ECCE	SICS	Phacoemulsification
Large 10-12 mm incision was required; sutures required	Large 7-8 mm incision; sutures required	Incision of 5-6 mm Sutures usually NOT required	Clear corneal or sclerolimbic incision of 3.2-3.5 mm is made. Sutures usually NOT required
Of historical interest only now Entire lens with its capsule was removed with a cryopencil/cryoprobe Dilation of pupil was NOT required. Could be done with loupe or microscope	Anterior can-opener capsulotomy or capsulorhexis is done Nucleus delivered by manual sliding Capsular bag is left behind for PCIOL implantation in the bag - "in the bag" is the ideal site for IOL implantation	Scierocorneal self sealing tunnel is made Rest same as ECCE; nucleus delivered by vectis, or viscoexpression	Capsulorhexis is a MUST ; next steps are hydrodissection and hydrodelineation Nucleus is emulsified with ultrasound energy - phaco- emulsification Phaco probe has hollow titanium needle PCIOL implanted (injected) in the bag

New Procedures

- **MICS**: Microincision cataract surgery, by definition, done through less than 1.5 mm incision.
- **Femto**: **femtosecond laser assisted cataract surgery**: femtosecond laser is used for corneal incisions, capsulorhexis and nucleus fragmentation; the nucleus pieces are removed with the phacoprobe - this is the closest to full "laser cataract surgery" at present.
- Femtosecond laser-wavelength 1053 nm; frequency 100 %.



Fig. 10.31: Anterior chamber intraocular lens



Figs 17.32: Single piece foldable PCIOL in-the-bag

CONGENITAL CATARACT SURGERY**Timing for Surgery of Congenital Cataracts**

- Small stationary lens opacities not interfering with vision can be ignored.
- **Complete bilateral cataracts** should be removed **as early as possible (within 4-6 weeks of birth)** to prevent stimulus deprivation amblyopia.
- **Complete unilateral cataracts** should also be removed **as early as possible (within days of birth)** and aggressive anti-amblyopia therapy given.

Surgery for Congenital Cataracts

- **Lens aspiration** is done followed by **IOL implantation**.
- **Lens aspiration with primary posterior capsulorhexis and anterior vitrectomy** (preferred in infants less than 2 years of age) - **reduces chances of PCO** (PCO is **nearly universal** if the posterior capsule is left intact in children < 6 years).
- Pars plana lensectomy with vitrectomy - NOT routinely preferred.
- **IOL implantation** is done in children whose ocular growth is complete - **usually > 2 years**; PCIOL in the bag is implanted.

COMPLICATIONS OF CATARACT SURGERY

Operative	Early post-operative (within 4 weeks)	Late post-operative (1 month to years)
Superior rectus muscle laceration during ' bridge ' suture Posterior capsular rupture and vitreous loss	Endophthalmitis Uveitis Corneal edema Raised IOP Wound leak Retained lens matter	Posterior capsule opacification (PCO) Endophthalmitis Cystoid macular edema

Contd

Contd

Operative	Early post-operative (within 4 weeks)	Late post-operative (1 month to years)
Posterior dislocation of nucleus Expulsive choroidal hemorrhage	Retinal detachment Toxic anterior segment syndrome (TASS)	Anterior capsule phimosis Displacement of IOL (sunset syndrome)

Remember

- **Most common complication** of cataract surgery is **PCO** (see below).
- **Most serious/dreaded/dangerous complication** of cataract surgery is **endophthalmitis** (see below).
- **Cystoid macular edema** after cataract surgery is called **Irvine Gass syndrome**; more incidence after posterior capsular rupture; **flower petal** appearance on FFA.
- **UGH syndrome: Uveitis, Glaucoma, Hyphema** syndrome - seen with anterior chamber IOL (ACIOL).
- **Cyanopsia**: Blue end of the spectrum is absorbed more by the cataractous lens, esp. nuclear cataracts; so patients may see objects 'blue' after cataract surgery - cyanopsia.

Posterior Capsule Opacification (PCO)

- **PCO = 'after cataract' or 'secondary cataract'** → occurs when the posterior capsule and part of the anterior capsule are left behind in situ (capsular bag for IOL implantation) as in modern day cataract surgery (i.e., after **extracapsular cataract extraction (ECCE)**, **sutureless small incision cataract surgery (SICS)** and **phacoemulsification**). The remnant part of anterior capsule continues to fulfill its function of forming new lens fibres - these fibres become opaque.
- **Soemmering's ring**: Sometimes, the lens fibres enclosed between the two layers of capsule form a dense ring behind the iris.
- **Elschnig's pearls**: The subcapsular equatorial cells proliferate and instead of forming lens fibres, develop into large balloon like cells (**Bladder cells**, **Wedl cells**) which fill up the pupillary aperture
 - PCO is more in **children, young patients, PMMA and hydrophilic lenses**
 - PCO is less in **hydrophobic acrylic lenses and square edge lenses**.
- In spite of the PCO however, **advantages of intact posterior capsule** after cataract surgery are: **decreased chances of cystoid macular edema, vitreous herniation and retinal detachment**.

- Treated by **Nd:YAG laser capsulotomy** which clears the membrane centrally.

EXTRA EDGE

- In **ICCE** (Intracapsular cataract extraction): The entire lens with its capsule is removed - not done in modern day cataract surgery - here PCO is obviously not seen.



Fig. 17.33: PCO, Posterior Capsule Opacification

Acute postoperative endophthalmitis

- **Incidence**: Following cataract surgery is about **0.15%**.
- **Etiology**:
 - **Coagulase negative staphylococci** (Staph, epidermidis) - **90% - MC**.
 - Others (Staph aureus, streptococcus and pseudomonas)
 - In **filtering bleb-associated cases (post-trabeculectomy)**, the MC is **Streptococcus**.
 - In **chronic postoperative endophthalmitis**, an important causative organism is **Propionibacterium acnes**, a **slow-growing**, gram-positive bacillus that is associated with a **characteristic white, intracapsular plaque**; fungus is also a cause (*Candida parapsilosis*).
- **Presentation**: **Pain, loss of vision after cataract surgery; chemosis, ciliary congestion, corneal haze, discharge, fibrinous exudate in anterior chamber, hypopyon vitritis** may be seen.
- **Treatment**: As per the **EVS (Endophthalmitis Vitrectomy Study)**:
 - **Intravitreal antibiotic injection** is the **mainstay**. injection, **Ceftazidime and injection, Vancomycin**.
 - Oral antibiotics are of uncertain benefit.
 - Topical antibiotics are of limited benefit.
 - Intravitreal steroids is controversial.
 - **Pars plana vitrectomy** indicated for patients with **vision of PL** (perception of light) and NOT for hand movements or better visual acuity level.
 - The only **proven prophylaxis** is the **instillation of povidone iodine** in conjunctival cul de sac.

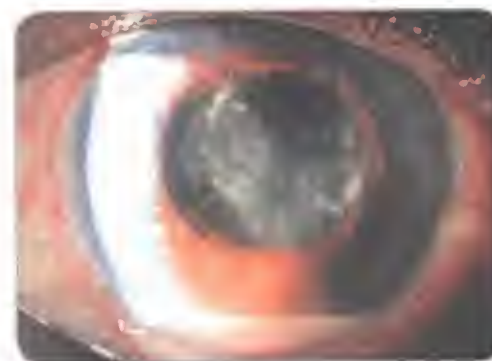


Fig. 17.34: Acute endophthalmitis

ECTOPIA LENTIS

Displacement of the lens from its normal position (in **pteller fossa**) results from partial or complete rupture of lens zonules. The lens may be **completely dislocated (luxated)** from the pupillary space or **partially displaced (subluxated)** and still remain in the pupillary area.

Etiology

- **Familial ectopia lentis: AD**.
- **Ectopia lentis et pupillae: AR**.
- **Marfan's syndrome**:
 - **AD**; mutation in **fibrillin gene** on chromosome **15q**.
 - Ocular: **Lens subluxation** that is **upward and temporally, bilateral**. Angle anomaly (secondary glaucoma); **retinal detachment** (due to lattice degeneration); flat cornea, pupil difficult to dilate; **blue sclera**; **axial myopia** maybe seen.
 - Systemic features: **arachnodactyly; hyperextensible joints; pectus excavatum; high arched palate; scoliosis and kyphosis; muscular underdevelopment (hernias); aortic dilation with dissecting aortic aneurysm; aortic regurgitation; mitral valve prolapse, dural ectasia**.
- **Homocystinuria**:
 - **AR**; decreased hepatic activity of **cystathionine synthase** results in accumulation of homocysteine and methionine.
 - Ocular features: **lens subluxation (downwards and inwards)**.
 - Systemic features: **tall slim build; osteoporosis; fair complexion; malar flush; mental retardation; increased platelet stickiness → thrombosis → hence general anesthesia is hazardous**.
 - Diagnosis is confirmed by detecting homocysteine in urine with **sodium nitroprusside**.

- **Weil Marchesani syndrome**:
 - Small and spherical lens (**microspherophakia**); **subluxation of lens (antero-inferiorly)**.
 - Angle closure glaucoma occurs when the small round lens blocks the flow of aqueous through the pupil. As this glaucoma is **aggravated by miotics and relieved by mydriatics**!! it is called **"inverse glaucoma"**.
 - **Short stature, brachydactyly (short stubby fingers), mental handicap**.
- Others: **Ehler's Danlos syndrome; Hyperlysinemia; Sulphite oxidase deficiency; Stickler syndrome**.
- **Traumatic displacement of lens: A/w blunt injuries**. **Couching** is an iatrogenic posterior dislocation of lens performed as a treatment of cataract in ancient days.
- **Spontaneous displacement of lens**: Results from intraocular diseases giving rise to mechanical stretching, inflammatory disintegration or degeneration of zonules. Seen in **high myopia, buphthalmos, hypermature cataract, staphyloma, intraocular tumors**.

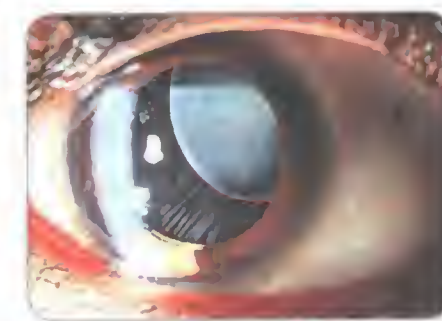


Fig. 17.35: Ectopia lentis

GLAUCOMA BASICS**Angle of the Anterior Chamber (AC)**

- **Structures in the angle of the AC** (seen by **gonioscopy**), from outside inwards (cornea side to iris side) are the
 - **Schwalbe's line** (a in Fig. 17.22)
 - **trabecular meshwork** (b)
 - **scleral spur** and (c)
 - **ciliary body band** (d)
- **Schaffer's, Scheie's and Spaeth's** gradings are used for grading AC angle
- **Trabecular meshwork** has 3 portions
 - **Uveal meshwork**: inner most portion
 - **Corneoscleral meshwork**: middle portion
 - **Juxtacanalicular meshwork**: outer portion; offers **major proportion of normal resistance to aqueous outflow**.

- **Angle of the anterior chamber** is seen by **gonioscopy**. The angle cannot be viewed directly without gonio lenses since the critical angle of the **cornea-air interface is 46 degrees** and leads to **total internal reflection**.
- **Gonioscopy** is not done (**NOT informative**) in **dilated pupils**.
- **Van Herick's method** is used to identify the "**openness of the angle**". With slit lamp beam oriented at 60 degree angle, the width of the **corneal section (C)** is compared with the **peripheral anterior chamber (PAC)** width.
- Normally **IgG is present in aqueous**.
- Increased **aqueous humor LDH** is seen in **retinoblastoma**.
- In comparison to plasma, aqueous has **Ascorbate** levels 20 times higher; is **slightly hyperosmotic** and has **low glucose and low protein**.
- ALSO KNOW: When compared to blood, **vitreous humor** also has high concentration of **ascorbate**.

Grade	C:PAC	Risk of angle closure	Angle width (degrees)
4	1:1	Impossible	35-40 (wide open)
3	1:1/2	Unlikely or improbable	20-35
2	1:1/4	Possible	20
1	1:<1/4	Likely or probable	10
0	No slit visible	Closed	0

AQUEOUS HUMOR

Aqueous Humor Secretion

- Secreted by **nonpigmented ciliary epithelium** by **active secretion (90%)**. Rest (10%) is by passive secretion (**ultrafiltration and diffusion**).
- **Rate of production is 2.6 micro l/min**.
- The ciliary epithelium contains enzyme systems that function in the production of aqueous humour. The enzymes **sodium-potassium activated adenosine triphosphatase [(Na+:K+)ATPase]** and **carbonic anhydrase** (catalyses conversion of CO_2 and H_2O into carbonic acid and H^+) participate in the active transport across this epithelium. Inhibition of these enzymes (**carbonic anhydrase inhibitors**) lowers intraocular pressure (IOP) by decreasing aqueous humor production.

Aqueous Humor Outflow

- **Trabecular (conventional) route**: accounts for **90% of outflow (major route)**.
- **Uveoscleral outflow**: accounts for 10% of outflow.
 - Increased by **prostaglandin analogs**; Decreased by **miotics**.

Aqueous Humor Composition

- **Specific gravity** = 1.002-1.004; **pH** = 7.1 - 7.3 (alkaline)

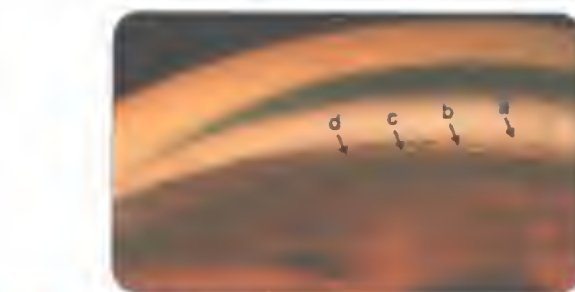


Fig. 17.36: Angle of the eye



Fig. 17.37: Gonioscopy

Intraocular Pressure (IOP)

- Normal IOP = 11-21 mmHg; **peaks in the early morning**
- For IOP measurement:
 - **Most accurate method = Manometry, but is impossible in clinical practice.**
 - **Gold standard clinical method = Goldmann's Applanation tonometer.**
 - Schlotz is indentation type tonometer - inferior to applanation tonometer.
 - **Non-contact tonometer** releases a **puff of air onto the cornea** and calculates the IOP by non-contact method.
- Relation of pachymetry (corneal thickness) and applanation IOP: **Thinner the cornea, higher the true IOP and vice versa - i.e., thinner cornea underestimates IOP.**
- **Facility of outflow of aqueous** is measured by **tonography** (tonometry measures IOP).

Types of Applanation Tonometers

Variable force/Constant area - A Contact Type

Goldmann tonometer: Considered to be the **gold standard**.
Perkins tonometer: **Hand held**. Similar to Goldmann.
Draeger tonometer: Hand held, Similar to Perkins.
Mackay-Marg tonometer: Electronically controlled plunger measures IOP; traced on a paper strip. No optical element.
 Tonopen: **portable, hand held**; useful in **irregular corneas**.
 Pneumotonometer.

Variable force/Constant area - B Non-Contact Type

Air-puff tonometer
Ocular Response Analyser (ORA) - useful for calculating **corneal hysteresis and biomechanics**

Variable area/Constant force - Contact Type

Maklakov tonometer

EXTRA EDGE

Non-applanating type, Contact tonometers

- **Dynamic Cantaur Tonometer (DCT, Pascal)** - **not affected by scleral rigidity**; useful **post-LASIK**.
- **Rebound tonometer (I-care)** - **no topical anesthesia required**; useful in children; useful for **SELF tonometry at home**.
- **Diaton tonometer - Trans-palpebral tonometer** (can measure over covered eyelids).

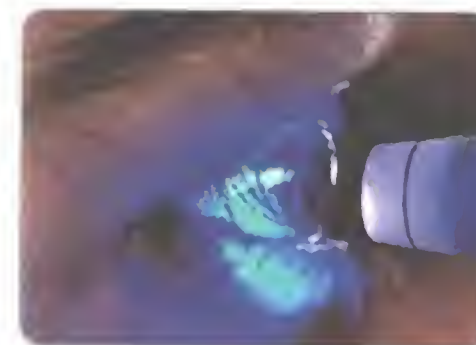


Fig. 17.38: Goldman applanation tonometry



Fig. 17.39: Parkins applanation tonometry



Fig. 17.40: Schiotz tonometry

Shallow Anterior chamber seen in	Deep anterior chamber seen in
Hypermetropia	Myopia
Narrow angle/angle closure glaucoma	Aphakia
Intumescent cataract	Keratoconus
Cornea plana	Buphthalmos
Anteriorly subluxated lens	Posteriorly subluxated lens
	Pigment dispersion syndrome

Causes of Colored Haloes

- Elevated IOP from any cause resulting in corneal epithelial edema - classically **acute congestive/acute angle closure glaucoma**, also **glaucomatocyclitic crisis** (Posner Schlossman syndrome) and **epidemic dropsy glaucoma**.
- **Corneal edema** from any cause (e.g. **Bullous keratopathy**).
- **Acute mucopurulent conjunctivitis** - due to mucus flakes on cornea scattering light.
- **Senile immature cataract** - due to scattering of light
- **Acute anterior uveitis** - due to hazy media
- **Epiphora**
- **Dirty contact lens usage**.

Fincham's test

Differentiates **colored haloes due to glaucoma** from that due to **senile immature cataract (SIMC)**. A stenopaic slit is passed in front of the eyes - **halo due to angle closure glaucoma remains intact** (but **diminished in intensity**), whereas halo due to SIMC is broken up/splits and then reunites.

CHILDHOOD GLAUCOMAS

Primary Congenital Glaucoma (PCG)

- Glaucoma that develops due to **developmental anomaly of the angle of the anterior chamber**, **not due to** any other ocular or systemic anomaly.



Fig. 17.43: Automated perimetry—Humphrey analyzer

- African/black race
- Neovascular or inflammatory glaucoma
- Combined surgery (with cataract extraction or other surgery)
- Previously failed trabeculectomy

Artificial Drainage Implants

- Also called glaucoma Shunts/Valves: **Molteno** implant, **Baerveldt** implant, **Alimed** glaucoma valve.
- **Indications:** failed trabeculectomies; neovascular glaucoma, anterior segment dysgenesis, conjunctival scarring near limbus.

Recent advances

- **SWAP: Short Wavelength Automated Perimetry;** Also called **Blue on Yellow perimetry** since the stimulus is blue and projected on a yellow background. Detects glaucomatous field defects earlier; BUT difficult to perform and interpret in eyes with denser cataracts.
- **FDT: Frequency doubling technology.** Useful as a **screening perimetry** for glaucoma and neurological fields.
- **ExPRESS shunt:** A **stainless steel** shunt used during trabeculectomy that allows one way flow of aqueous humor out of the anterior chamber; helps to **prevent hypotony**.
- **Trabectome:** a handpiece (similar to phaco handpiece) sunroofs Schlemm's canal and ballates the trabecular meshwork thereby improving aqueous drainage.
- **Canaloplasty:** A nylon suture is threaded through Schlemm's canal and sutured in place to help the aqueous to drain better.
- **Non-penetrating glaucoma surgery:** here the anterior chamber is not penetrated/entered so that associated complications are lesser; the procedures are **deep sclerectomy** and **viscoconalostomy**.

Ocular Hypertension

- The term ocular hypertension is used when the **IOP is found to be over 21 mmHg on two consecutive visits**, in the **absence of glaucomatous optic nerve head changes or visual field loss**.

Normal Tension Glaucoma

- Also called **low tension glaucoma**, describes a type of POAG that is characterized by the following:
 - A mean **IOP equal to or less than 21 mm Hg** on diurnal testing with no single measurement greater than 24 mmHg.
 - Glaucomatous optic **disc damage and visual field loss**

- **Open angle** on gonioscopy
- Progressive glaucomatous damage
- Absence of secondary causes for glaucomatous optic disc damage.
- NTG is believed to result from **chronic low vascular perfusion (due to hypotension, CVS disease)** that makes the optic nerve head susceptible to damage by normal IOP.
- Characteristics more common in patients with NTG are:
 - NTG is **MC in Japan**; Optic nerve head is **larger**; incidence of **splinter (Drance) hemorrhages at disc**

margin; visual field defects are denser and closer to fixation (i.e., closer to centre).

- **Peripheral vascular spasm** on cooling; **migraine** headaches; **nocturnal systemic hypotension**; **over-treated systemic hypertension**; **reduced blood flow velocity in the ophthalmic artery**; **paraproteinemia** and presence of serum autoantibodies.
- **Treatment:** By **IOP lowering drugs and trabeculectomy** if necessary; most of the times treatment may be unsatisfactory and progression may occur.

ANTI GLAUCOMA DRUGS

Mechanism of action	Examples	Side effects
β-Adrenergic blockers		
MOA: by reducing aqueous production	• Timolol: (0.25 or 0.5%), is the MC used.	SE: All side effects of systemic beta blockers apply to topical beta blockers as given below
If patient is already on systemic beta blocker, topical beta blocker may NOT offer much extra benefit to lower IOP; use other drug instead.	• Betaxolol: (0.25 or 0.5%), β1 selective (cardioselective), preferred in asthmatics	
	• Levobunolol	
	• Carteolol	
	• Metipranolol (causes granulomatous anterior uveitis)	
Side effects of beta blockers		
Ocular side effects	Systemic SE	Contraindications
• Itching and burning in eye	Bronchospasm	Reactive airway disease (asthma, COPD)
• Dryness of eyes	Bradycardia and heart block	Congestive heart failure
• Allergic blepharo-conjunctivitis	Worsening of CHF,	Bradycardia
• Corneal hypoesthesia	Nightmares, disturbed sleep	Variant (Prinzmetal's angina)
• Blurred vision	GI disturbances, fatigue,	Peripheral vascular disease
• Superficial punctate keratitis	Impotence	Elderly
• Punctal stenosis and acquired nasolacrimal duct obstruction	Blood dyscrasias	
	triglycerides, HDL cholesterol	

2 Miotics

- MOA: They increase aqueous outflow facility.
- **Pilocarpine** (1,2, 4 %); 2% 4 times daily is MC used.
- SE: **Induced myopia**; pupillary constriction that compromises vision in patients with cataract; **headache/brow pain**; **retinal detachment**; **iris cysts**

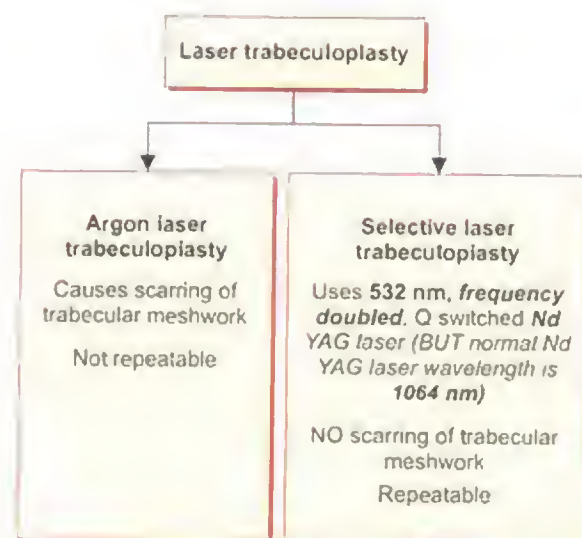
4 Adrenergic agonists (Sympathomimetics)

- MOA: reduce aqueous production (main action); also increase aqueous outflow
- **Brimonidine:** more selective α2 agonist; MC used
- **Apraclonidine:** α2 agonist; used for controlling acute rises in IOP (such as after laser trabeculoplasty or laser iridotomy)
- **Epinephrine:** poor corneal penetration, NO longer used.
- **Dipivefrine,** is a prodrug of epinephrine; penetrates cornea better; NO longer used.
- SE: Epinephrine (**maculopathy**, black **adrenochrome** deposits); apraclonidine and brimonidine (**allergic follicular conjunctivitis**, **blepharitis** and **eyelid retraction** – both MC with apraclonidine); brimonidine (**dry mouth**, **drowsiness**, **apnea in children < 6 years**)

4 Topical carbonic anhydrase inhibitors (CAI)

Treatment

- **Medications** in glaucoma: See detailed table below.
- **Laser Trabeculoplasty:** useful in **POAG**; **Pseudoexfoliation glaucoma**; **Pigmentary glaucoma**; It involves **laser application to the trabecular meshwork to enhance outflow of aqueous humor**. It is **NOT useful in angle closure glaucoma and uveitic glaucoma** since the trabecular meshwork is not visible in these cases.



- **Surgery:** **Trabeculectomy** is the **gold standard surgery for lowering IOP** so far. The use of **antimetabolites (Mitomycin C and 5-FU)** helps to **minimize subconjunctival and episcleral scarring** and hence the bleb functions better to keep the IOP low.
- Indications for use of antimetabolites are:
 - Younger patients

Conid...

Mechanism of action	Examples	Side effects
MOA: Reduce aqueous formation.	<ul style="list-style-type: none"> • Dorzolamide • Brinzolamide: lesser side effects 	SE: Bitter taste, eye irritation; contraindicated in patients with sulfonamide allergy since CA are sulfa derivatives; relatively contraindicated in keratoplasty patients/corneal disorders
5. Prostaglandin analogs		
MOA: increasing uveoscleral outflow	<ul style="list-style-type: none"> • Latanoprost • Bimatoprost • Travaprost – all used once daily. • Unoprostone used twice daily. • Tafluprost 	SE: Conjunctival congestion (least with latanoprost); darkening of iris (hyperchromia) and periorbital skin , increase in length of eyelashes , mild iridocyclitis ; cystoid macular edema in aphakics ; relatively Contra-Indicated in uveitis patients.

EXTRA EDGE

- **Brimanidine** is the only glaucoma drug belonging to "category B" in pregnancy (presumed safety based on animal studies); **all other** glaucoma drugs are "category C" drugs (uncertain safety from the lack of human studies and reported adverse effects in animal studies).
- Also note that in narrow angle glaucoma - drugs which dilate the pupil such as atropine and homatropine etc. should not be used.

Systemic Agents

- Systemic Carbonic anhydrase inhibitors:
 - **Acetazolamide**: useful in acutely controlling raised IOP; **contraindicated in those with sulfa allergy** (Steven Johnson syndrome); can cause parasthesiae, malaise, diarrhea/nausea, renal stones, blood dyscrasias.
- Hyperosmotics:
 - Used to **acutely control raised IOP** prior to surgery or in acute congestive glaucoma etc...
 - Contraindicated in cardiac and renal disease (can increase extracellular volume and cause cardiac overload); urinary retention in elderly men may occur.
- **Mannitol**: Intravenous, most widely used.
- Oral **glycerol**: sweet sickly taste, to be taken with lime juice; caution in diabetics.
- **Isosorbide**: oral, minty taste, can be used in diabetics.

PRIMARY ANGLE CLOSURE GLAUCOMA

- **Etiology**: MC in fifth decade of life; **M:F=1:4**; emotional nervous people with unstable vasomotor system are more affected; **first-degree relatives** are at increased risk; MC in south-east Asians, Chinese and Eskimos but uncommon in blacks.

- **Anatomical risk factors**: **hypermetropic eyes with shallow AC**; eyes with narrow angle of the AC which may be due to **small eyeball, smaller cornea, bigger size of the lens or bigger size of the ciliary body**.
- Main Mechanism of angle closure: **Pupillary block mechanism**.

Stages of Angle Closure

- Latent Glaucoma (Prodromal Phase)
 - **Clinical features**: Transient rise of IOP upto **40-60 mm Hg**; eye remains white and without congestion; **AC depth is shallow and gonioscopy reveals narrow angle**; transient blurring of vision, **colored haloes** around light due to corneal edema and mild head ache may occur.
 - Treatment: Both eyes prophylactic YAG laser peripheral iridotomy.
- Intermittent Glaucoma (Stage of Constant Instability)
 - Occurs in a **predisposed eye with occludable angle** in association with intermittent pupillary block. Physiological mydriasis (watching TV in dark room) or physiological shallowing of AC when the patient assumes a prone/semiprone position (when sewing/reading) → rapid closure of the angle → a sudden increase in IOP (few minutes to 1-2 hours) → physiological miosis (bright light/sleep) breaks the attack → IOP returns to normal levels.
 - **Clinical features**: Blurring of vision; **haloes around lights (blue/violet innermost)**; eyeache/ frontal headache. During an attack eye is usually uncongested and in between attacks it looks perfectly normal although the angle is narrow.
 - Treatment: both eyes prophylactic YAG laser peripheral iridotomy.

Acute Congestive Angle Closure Glaucoma (Acute Angle Closure Glaucoma)

History

- H/O watching TV in dark (causes mid-dilated pupil position which is ideal for pupillary block), followed by sudden onset of symptoms; H/O **colored haloes**

Clinically

- Sudden onset **blurred vision, eye pain, headache, nausea, and vomiting, photophobia**, watering, **acute red eye**
- May have previous history of **colored haloes** (red outside, violet innermost)
- **Ciliary congestion**, **corneal edema/hazy/steamy cornea**, **shallow anterior chamber**, **mid-dilated vertically oval fixed pupil**, very high IOP; **fellow eye has shallow anterior chamber**

Treatment

- Reduce IOP with – IV Mannitol and oral acetazolamide initially; Start **pilocarpine** once IOP is < 40 mm Hg so that iris ischemia is reduced and allows pilocarpine to act; beta blockers (timolol), alpha agonists (brimonidine); topical steroid drops.
- As soon as cornea clears do **Nd YAG laser PI** (to both eyes) – **definitive treatment**.
- Vogt's triad: **diagnostic of previous attack of acute congestive glaucoma** and is characterized by:
 - **Glaucoma flecken** (anterior subcapsular lens opacity in pupillary zone)
 - Patches of **iris atrophy**
 - Slightly dilated non reacting pupil (due to sphincter atrophy)
- Chronic Congestive Stage
 - Also called '**creeping angle closure**' as the angle becomes slowly and progressively closed.
 - Clinical features: VA is always impaired; chronically congested and irritable eye; glaucomatous optic disc cupping; peripheral anterior synechiae develop; visual field defects as in POAG appear.
 - Treatment: After lowering IOP, **trabeculectomy** should be performed; laser iridotomy to the other eye is done.

Provocative Tests (NOT Done Routinely)

- Tests for **PACG** suspects designed to precipitate and attack of angle closure glaucoma in the ophthalmologist's clinic where it can be treated promptly.
- **Prone dark room test**: most popular and best physiological provocative test for PACG suspects. Before test IOP is recorded, then patient is made to lie prone in a dark room for one hour (remains awake so that pu-

pil is dilated), after 1 hour IOP is again measured. An increase in IOP of more than 8 mmHg is considered diagnostic of PACG.

2. **Mydriatic provocative test**: not preferred now.

ISGEO classification

International Society of Geographic and Epidemiological Ophthalmology classification is a clinically applicable classification of angle closure glaucoma.

- **Primary Angle Closure Suspect (PACS)**: Presence of appositional closure between peripheral iris and posterior trabecular meshwork (**occludable angles**) in 3 or more quadrants, BUT normal IOP, disc and fields.
- **Primary Angle Closure (PAC)**: PACS with signs of trabecular meshwork obstruction, i.e. peripheral anterior synechiae, elevated IOP, excessive pigmentation in angle, glaucoma flecken or iris whirling; BUT optic disc is healthy.
- **Primary Angle Closure Glaucoma (PACG)**: PAC with damage to optic disc and/or visual field changes.

Plateau Iris

- **Plateau iris configuration**: Anterior iris insertion causing shallow peripheral angle and may have normal central anterior chamber depth.
- **Plateau iris syndrome**: Plateau iris with narrow angles persisting after laser PI; may have acute angle closure glaucoma inspite of a patent PI.
- **Double hump** sign and **sine wave** sign are seen on gonioscopy.

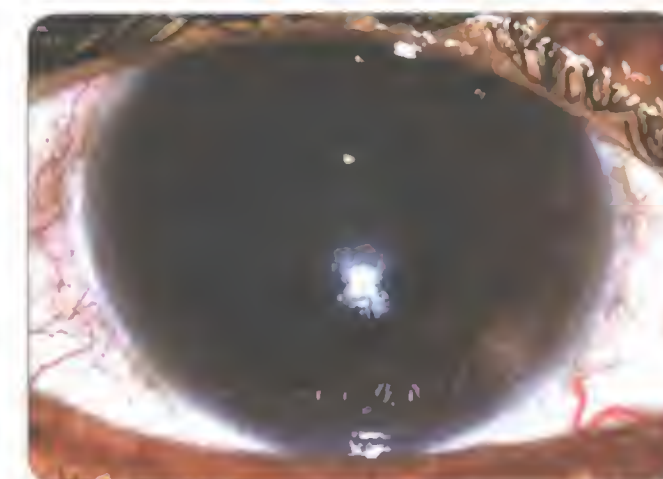


Fig. 17.44: Acute congestive glaucoma

LENS-RELATED GLAUCOMAS

Phacolytic glaucoma (<i>lens protein glaucoma</i>)	Acute Secondary Open angle glaucoma due to leakage of lens proteins through microscopic defects in the intact capsule of a hypermaturing cataract ; Macrophages, laden with phagocytosed lens material, block the trabecular meshwork and obstruct aqueous outflow. Presents with headache, vomiting, eyepain, redness, poor vision, corneal edema, DEEP Anterior chamber (AC) , OPEN angles , flare/refractile matter in AC, pseudohypopyon (in severe cases) and Raised IOP. Treatment: Lower IOP, cataract extraction and thorough AC wash is the definitive treatment .
Lens Particle Glaucoma	Secondary open angle glaucoma due to obstruction of the trabecular meshwork by free particulate lens material released due to disruption of the lens capsule either by cataract extraction or due to penetrating injury. Treatment: Lower IOP medically and Irrigation aspiration of lens matter from AC or by vitrectomy (if associated with PC rupture).
Phacomorphic glaucoma	Acute secondary angle closure glaucoma a/w Intumescent cataract ; presents with high IOP, SHALLOW AC , corneal edema, pain. Treatment: Extraction of cataract after lowering IOP
Phacoanaphylactic glaucoma	Autoimmune granulomatous reaction to lens proteins (due to previous sensitization to lens proteins due to earlier cataract surgery or penetrating injury or due to nucleus retained in vitreous). Treatment: Lower IOP medically and corticosteroids for control of inflammation and extraction of lens matter if any
Phacotopic glaucoma	Dislocation of the lens into the AC blocking the angle completely giving rise to secondary angle closure glaucoma

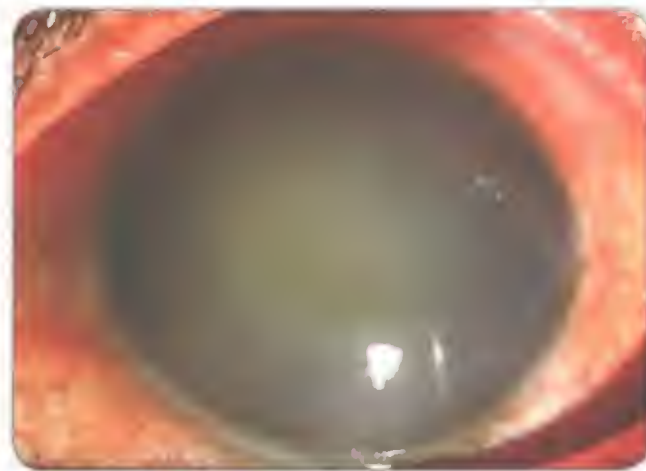


Fig. 17.45: Phacolytic glaucoma

- **Intravitreal Avastin (bevacizumab)** is also used for **new vessels regression**;
- If IOP uncontrolled - **trabeculectomy with antimetabolites** or artificial valve.

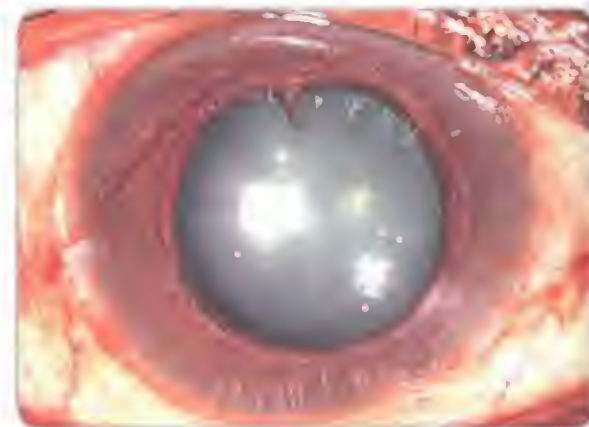


Fig. 17.46: Rubeosis Iridis

OTHER IMPORTANT GLAUCOMAS

Neovascular Glaucoma

- Secondary glaucoma a/w neovascularization of the **iris and angle** of the AC (**rubeosis Iridis**).
- Etiology: **diabetic retinopathy**; **ischemic CRVO** ("**90 day**" glaucoma); **sickle cell retinopathy**; **retinopathy of prematurity**; **chronic intraocular inflammation**, **intraocular tumors**, **long standing RD**, **CRAO**, **carotid obstructive disease**.
- Treatment: **Panretinal photocoagulation (PRP)** is **mainstay** to prevent further neovascularization;

Steroid-induced Glaucoma

- A **secondary open angle glaucoma** that develops following **topical (more commonly)** and sometimes **systemic steroid therapy**.
- **Risk factors for steroid response**: individuals who have **POAG**; or family history of **POAG**; **Myopia**; **younger patients**; **connective tissue disease**, **african americans**.
- **Note**: If **acute rise in pressure**, **pain** and **coloured haloes** may occur.

Ciliary Block (Malignant) Glaucoma

- Classically occurs following **filtering surgery (trabeculectomy)** or peripheral iridectomy and following cataract surgery (aphakia or pseudophakia).
- Characterized by **flat AC after intraocular surgery**; **markedly raised IOP**, **negative Seidel test** (no wound leak), and poor response to conventional medical therapy. **PI should be patent before making diagnosis of malignant glaucoma**.
- **Mechanism**: **cilio-lenticular block** or **cilio-vitreous block** - leading to aqueous pockets in the vitreous— "**aqueous misdirection syndrome**".
- **Treatment**: **Mydriatics** (phenylephrine) and **cycloplegic** (1% atropine) If no response in 4-5 days, **posterior sclerotomy** to aspirate fluid from the vitreous and injection of air into the AC is required.

Glaucomatocyclitic Crisis (Posner Schlossman synd.)

- **Unilateral** disease of **young adults** (40% positive for HLA-BW54)
- Recurrent attacks of **acute secondary open angle glaucoma** a/w **mild anterior uveitis** (hypertensive uveitis). Cause of raised IOP is **acute trabeculitis**.
- **White eye** (minimally congested), **corneal epithelial edema** (**colored haloes**), **few fine white central KPs**, **IOP is usually very high**, few aqueous cells may be present.

Glaucoma Associated with Iridocorneal Endothelial (ICE) Syndromes

- The three **ICE syndromes** are:
 - **Progressive iris atrophy**: iris features predominate with **corectopia** (distortion of pupil) and **polycoria** (multiple pupils).
 - **Chandler's syndrome**: **Corneal edema** predominates.
 - **Cogan-Reese syndrome**: **nodular or diffuse pigmented iris lesions** are present.
- ICE syndrome typically affects **one eye of young to middle aged women**.
- Common feature of ICE syndromes = **abnormal corneal endothelial cells** ("**hammered silver**" appearance) that proliferate to form an endothelial membrane in the angle of the AC.
- **Treatment**: **Medical treatment is ineffective** usually; **trabeculectomy with antimetabolites**; or **glaucoma valves/shunts** is needed.

Absolute Glaucoma

- Absolute glaucoma is the **final end stage result** of any type of glaucoma.

- **Clinical features**: **Painful, irritable and extremely high IOP** (**stony hard**) and **no PL** - **painful blind eye**.
- Complications **corneal ulceration**; **staphyloma formation**, **atrophic bulbi**.
- **Treatment**: Destruction of secretory ciliary epithelium by **cyclocryotherapy** or **transcleral diode laser cyclophotocoagulation (TSCPC)** or **endoscopic cyclophotocoagulation**; **enucleation of eyeball** if all other methods fail.

Various other glaucoma

Pseudoexfoliation glaucoma

Whitish powdery material at pupillary margin (**pupillary powdering**) and on lens surface (**3-ring sign**), **pupillary ruff** defects, **poor pupillary dilation**, **pigment along Schwalbe's line** - **Sampolaes's line**, higher incidence of **zonular dehiscence** and **vitreous loss** during cataract surgery.

Pigmentary glaucoma

Pigments on corneal endothelium (**Krukenburg's spindle**), **concave iris configuration**, **deep AC**, **hyperpigmented open angle** with, **mid peripheral iris transillumination**, **young myopic males** are predisposed; **YAG laser PI** to relieve the '**reverse pupillary block**'.

Angle recession glaucoma

Seen after **blunt trauma** to eye as an **irregular widening of the ciliary body band** on gonioscopy.

Hypersecretion glaucoma

Epidemic dropsy glaucoma, bilateral white eyes with **very high IOP** with **colored haloes**;

UGH syndrome

Uveitis, Glaucoma, Hyphema syndrome a/w **anterior chamber lens (ACIOL) implantation**.

Ghost cell glaucoma

An open angle glaucoma that occurs in **aphakic eyes with vitreous hemorrhage**. After about 2 weeks of hemorrhage, **RBCs** degenerate, lose their pliability and become **khaki colored (ghost cells)** which pass from the vitreous cavity into the AC and block the trabeculae leading to rise in IOP

Glaucoma due to increased episcleral venous pressure **Sturge weber syndrome**; **carotico-cavernous fistula**

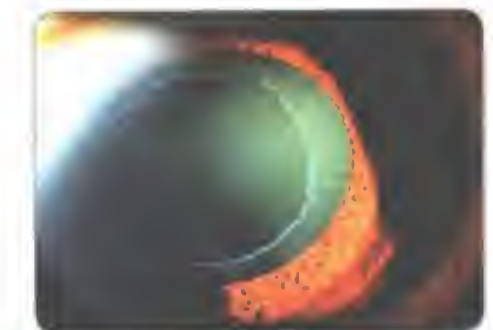


Fig. 17.47: 3-ring sign in pseudoexfoliation syndrome

UVEITIS

(Uvea = Iris + Ciliary Body + choroid)

Iris

- **Sphincter pupillae muscle (parasympathetic, miosis).**
- **Dilator pupillae muscle (sympathetic, mydriasis)**
- Pigment epithelium: Consists of 2 layers of cells: *anterior layer and -posterior layer* which is *continuous with the pigment epithelium of the ciliary body and RPE of the retina*, all having same embryologic origin.
- **Circulus iridis major** is seen at the **root of the iris**.

Ciliary Body

- Ciliary body extends for 6 mm from the end of the retina (ora serrata) till the scleral spur.
- It consists of **anterior portion (pars plicata)** and **posterior portion (pars plana)**.
- Pars Plicata has 60–70 folds called the **ciliary processes**, which secrete the aqueous humor into the posterior chamber (from **nonpigmented ciliary epithelium**).
- Note: The **pars plana** is the area through which **vitrectomy surgical instruments** are usually introduced.
- Ciliary muscle has 3 parts all under parasympathetic innervation:
 - Longitudinal (Outermost)
 - Radial
 - Circular
- **Contraction of the radial and circular muscles relax the zonules** allowing for increased curvature of the lens, thereby increasing its refractive power in the process of **accommodation** (near vision).
- **Contraction of the longitudinal muscle** stretches mainly the choroid but also applies forces on the scleral spur thereby **opening the canal of Schlemm and facilitating the aqueous drainage**. **Pilocarpine** is a cholinergic drug clinically used to decrease intraocular pressure in glaucoma patients, by the above mechanism.

The Choroid

- Dark brown **vascular sheet**, 0.25 mm thick, lying between the sclera and the retina.
 - outer vascular bed have large vessels (**layer of Haller**)
 - Inner bed consists of an extensive network of fenestrated vessels, the **choriocapillaris** which is the **major blood supply to the outer layers of the retina and to the whole macula** (the inner layers, up to the middle of the outer plexiform layer are supplied by the central retinal artery).

Bruch's Membrane

- A relatively thin (1–4 microns) and refractile connective tissue membrane lying **between the choriocapillaris and the choroid and the RPE of the retina**.
 - Also called lamina vitrea.
 - composed of 5 different layers by electron microscopy.
- In AMD (age related macular degeneration), there are yellow depositions in Bruch's membrane called drusens, usually at the macula.

Aqueous Flare

- **Protein transudation** from the iris/ciliary vessels produces an opalescence of the aqueous, an **aqueous flare**, which may be visible on oblique view of slit lamp with its beam narrowed to 2 X 1 mm. Occurs due to **Tyndall effect**.

Grade	Flare
0	Absent
1 +	Faint, barely detectable
2 +	Moderate, iris and lens details clear
3 +	Marked, iris and lens details hazy
4 +	Intense flare, fibrinous aqueous

Aqueous cells	
Grade	Cells in the field (1 mm × 1 mm slit beam)
0	< 1
0.5	1–5
1+	6–15
2+	16–25
3+	26–50
4+	> 50

Definitions

1. **Uveitis:** An inflammation of the uveal tract, which may also involve the adjacent structures.

2. Endophthalmitis

- Inflammation affecting inner portions of the globe (retina, choroid and ciliary body – uvea) and adjacent cavities (anterior chamber, vitreous), **SPARING THE SCLERA**
- Clinically it usually means vitreous involvement

3. Panophthalmitis

- A suppurative endophthalmitis that **SPREADS TO INVOLVE the sclero, episclera, Tenon's capsule and orbital tissues** (including extraocular muscles, orbital fat etc.)
- It involves **all three coats of the eyeball**
- **Enucleation is contraindicated**

CLASSIFICATION OF UVEITIS

1. **Anatomical Classification (IUSG, International Uveitis Study Group Classification and SUN, Standardization of Uveitis Nomenclature)**
 - **Anterior uveitis:** Inflammation of the iris (iritis), anterior part of ciliary body (cyclitis), or both (iridocyclitis).
 - **Intermediate uveitis:** Inflammation of the posterior part of ciliary body and pars plana (pars planitis).
 - **Posterior uveitis:** focal or diffuse choroiditis, retinitis, retinochoroiditis, chorioretinitis and neuroretinitis.
 - **Panuveitis:** involvement of all - anterior chamber, retina, vitreous and choroid.
2. **Clinical Classification**
 - **Acute uveitis:** Onset = sudden, Duration < 3 months.
 - **Chronic uveitis:** Onset = insidious, duration > 3 months; OR relapse within 3 months of stopping treatment.
 - **Recurrent uveitis:** recurrent attacks of inflammation.
3. **Pathological Classification**
 - Non granulomatous uveitis
 - Granulomatous uveitis

Granulomatous Uveitis	Nongranulomatous Uveitis
Insidious onset and chronic course	Acute onset and short course
Relatively mild and white eye	Severe and red eye
Nodules (Koeppe's and Busacca's) on Iris	No such nodules
Medium to large keratic precipitates (KP's, often 'mutton fat' type)	Fine KPs
Mild flare	Intense flare often with heavy fibrinous exudates
Anterior uvea (iris, ciliary body) and retina-choroid equally involved	Mainly limited to anterior uvea
TB, sarcoidosis, leprosy etc. are usually responsible	Mainly Idiopathic and allergic in nature

4. Etiological Classification

- **Infectious:** Bacterial, Viral, Fungal, Parasitic, Others
- **Non-Infectious:** Known systemic association, No known systemic association
- **Masquerade:** Neoplastic, Non-neoplastic.

ANTERIOR UVEITIS (IRIDOCYCLITIS)

Symptoms

- **Pain**—acute, severe, with radiation along the branches of the fifth nerve, typically worse at night.
- **Redness and Dimness of vision**

Signs

- **Circumcorneal (ciliary) congestion.**
- Anterior chamber
 - **Aqueous flare** (flare is not necessarily indicative of active inflammation).
 - **Aqueous cells**—are **indicative of activity of uveitis**; it is due to exudation of inflammatory cells into the aqueous.
 - **Aqueous fibrinous** exudate: in **HLA B27** ass. Uveitis.
 - **Hypopyon**—classically seen in **Behcet's syndrome**; Also in **or herpetic uveitis** (hypopyon mixed with blood).
 - **HypHEMA**—in **herpetic uveitis** and trauma.

Keratic Precipitates

- **Keratic precipitates** are cellular deposits on corneal endothelium.
- **Arlt's triangle:** The inflammatory cells are wandering in the aqueous by **convection current** and stick to the edematous endothelial cells of the cornea - in a **base down triangular** area at the lower part of the cornea - Arlt's triangle.
- **Small KP's** (lymphocytes + plasma cells) in non-granulomatous uveitis.
- **Large KP's** (macrophage + epithelioid cells) in granulomatous uveitis (as in TB, sarcoidosis).
- **Fresh KP's** are round, white, fluffy and hydrated.
- **Old KP's** are shrunken, faded and become pigmented with crenated edges.
- Old **"mutton fat" KP's** have 'ground-glass' appearance.
- **Red KPs:** in **hemorrhagic uveitis**

- **Depth of AC**—deep and irregular in posterior synechiae; **funnel shaped in iris bombe**.
- **Iris**
 - Muddy iris; Iris nodules (in granulomatous uveitis).
 - **Koeppe's nodules** at the Pupillary border and smaller in size.
 - **Busacca's nodules** on the Surface of the Iris away from the pupil.
 - Iris atrophy and heterochromia—seen in Fuch's heterochromic cyclitis and herpetic uveitis.

- **Rubeosis Iridis**—in chronic anterior uveitis and Fuch's heterochromic cyclitis.
- **Synechia**
 - Posterior synechia—is the adhesion between the anterior lens surface and iris.
 - **Ring (annular) synechia**—posterior synechia extending for 360° around the pupil (**seclusio pupillae**) prevents the passage of aqueous from the posterior to the anterior chamber. This gives rise to forwards bowing of the iris causing an "**iris bombe**"—secondary glaucoma.
 - Peripheral anterior synechia—adhesion of iris with the corneal endothelium due to iris bombe.
- **Pupil**
 - Sluggishly reactive pupil; **miotic**.
 - **Festooned pupil** is due to **irregular** dilatation of pupil with mydriatic and is due to posterior synechia.
 - **Occlusio pupillae**, when the pupil is blocked by organized fibrinous exudates.
- Lens; **complicated cataract**.
- IOP may be normal, decreased (in acute iridocyclitis due to ciliary shock); increased in long standing anterior uveitis (due to secondary angle closure or may be steroid induced).
- Posterior segment—vitreous opacities and cystoid macular edema.

Sequelae and Complications of Anterior Uveitis

- Secondary glaucoma (**MC complication**)
- Cyclitic membrane
- Complicated cataract
- Cystoid macular edema.
- Phthisis (atrophic) bulbi: prolonged cyclitis → ciliary body atrophy → less secretion of aqueous → atrophic bulbi.
- Tractional RD—due to traction by cyclitic membrane
- Band shaped keratopathy—in children with JRA and chronic iridocyclitis.

Treatment

- **Mydriatic cycloplegic drugs**: Atropine sulfate eye ointment 1%, 2% homatropine or 1% cyclopentolate eye

- drops; **mydricalne** (a mixture of atropine, adrenalin and procaine given subconjunctivally).
- Corticosteroids
 - Topical; Systemic (oral, IV); Periocular (posterior subtenon's injection); Intravitreal steroid injection (triamcinolone acetonide)
 - Relieve **secondary glaucoma** with tab. acetazolamide and IOP lowering drugs (**AVOID** latanoprost and pilocarpine since both can worsen the uveitis).
 - **Cataract extraction** is done when the eye is quiet for at least 3 months.
- **Antimetabolites**: Azathioprine, Methotrexate and Mycophenolate mofetil.
- **Calcineurin inhibitors**: cyclosporine and tacrolimus.
- **Biological blockers**
 - Interleukin receptor antagonists: daclizumab and anakinra.
 - TNF alpha antagonists: infliximab and adalimumab

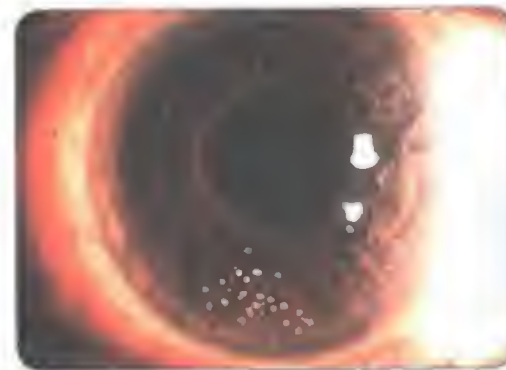


Fig. 17.48: Keratic precipitates

EXTRA EDGE

- **Drug of choice** for iridocyclitis/uveitis is a controversial question asked in the past—hope its not asked in future - If you have to select one option—go for "steroids" rather than "atropine", BUT both are essential for treatment; if you have a uveitis patient and treat him with steroid drops ONLY, he will be symptomatically better (reduced inflammation); If you give atropine drops ONLY, you are sure to get a call in the night for the pain (which would not have reduced!).

SPECIAL UVEITIS ENTITIES

Pars Planitis (Intermediate uveitis)	Affects children and young adults ; usually bilateral; causes Floater and blurring of vision	Snowball opacities in vitreous cavity; snow-bank exudates over pars plana – MC inferiorly
Posterior Uveitis	Floater and impaired vision Vitreous changes (opacities and PVD); Choroiditis and Retinitis (white cloudy retina). Vasculitis —affects retinal veins (periphlebitis) commoner than arteries (periarteritis)	

Contd.

HLA B27 ass. uveitis	Anterior uveitis, nongranulomatous	Ankylosing spondylitis (MC) , Reiter's syndrome, Inflammatory bowel disease (Crohn's, Ulcerative colitis), psoriasis
Juvenile RA associated uveitis	Anterior uveitis asymptomatic, non-granulomatous, ' white iritis ', endothelial dusting by KPs, posterior synechia are common. No symptoms, calcific band keratopathy .	Pouciorticular – early onset, usually in girls aged 4–6, uveitis is common (20%); Polyarticular (uveitis in ONLY 5%); Systemic JRA (Still's disease – NO uveitis).
Sarcoidosis	Anterior uveitis, granulomatous , intermediate uveitis, choroiditis, snowball or cotton ball opacities in vitreous, condle wax drippings or en toches de bougie (periphlebitis), Lander's sign (sarcoid nodules in retina)	Hilar adenopathy, restrictive lung disease, erythema nodosum
Fuch's heterochromic iridocyclitis	Anterior uveitis, nongranulomatous, minimal symptoms , iris heterochromia , white stellate KP's all over corneal endothelium , bridging vessels in angle of eye (which can bleed during AC paracentesis – Amsler's sign)	NO gross systemic symptoms, affects young people unilaterally , cataract common (good results with cataract surgery), prone to develop POAG
CMV retinitis	Posterior uveitis "Pizza pie"/"Cottage cheese and Tomato ketchup" appearance , "frosted branch onglitis" due to periphlebitis, "brushfire" extension	AIDS , Increased risk when CD4 < 50 ; Quantitative nucleic acid detection (QNAT) by PCR of intraocular fluid is inv. of choice. Treat with IV ganciclovir , foscarnet , cidofovir ; Intravitreal ganciclovir , fomvirsen , cidofovir .
Toxoplasmosis	Obligate intracellular protozoa MC cause of posterior uveitis Causes floater's, vitritis causing "headlight in fog" appearance, chorioretinitis . Superficial necrotizing retinochoroiditis adjacent to pigmented chorioretinal scar – satellite lesions . Papillitis may be secondary to active retinitis located in the juxtapapillary area (Jensen chorioiditis).	Congenital toxoplasmosis – 3C's – Convulsions , Calcifications , Chorioretinitis Treatment : Systemic steroids; Clindamycin; Sulphonamides; Pyrimethamine; Co-trimoxazole; Azithromycin; Atovaquone.
Herpes Zoster Uveitis	Nongranulomatous; severe iris ischemia → causes hypopyon mixed with blood .	Sectoral iris atrophy may be seen;
Toxocarasis	Toxocara is an Intestinal roundworm of cats (<i>Toxocara cati</i>) and dogs (<i>Toxocara canis</i>). Human ocular toxocarasis is caused by accidental ingestion of food contaminated by feces of pet cat or dog . Presents between the age of 2–9 years with leukocoria, squint or unilateral visual loss.	Signs : chronic endophthalmitis like picture (poor visual prognosis); posterior pole granuloma or a peripheral granuloma (excellent visual prognosis).
Onchocerciasis	Onchocerca volvulus helminth; vector is Simulium blackfly ; causes "River blindness"	Sclerosing keratitis, anterior uveitis, live floating microfilariae in AC may be seen; chorioretinitis; Treat with Ivermectin .
Cysticercosis	By Cysticercus cellulosae larval form of pork tapeworm Taenia solium ;	Cyst in subconjunctival space , orbit or extraocular muscles ; free floating cyst in AC may be seen, subretinal cyst causes RD; cyst in vitreous – toxic to eye. Treatment : Surgical removal of larvae from AC, vitreous and subretinal space. For other location systemic albendazole .
DUSN (Diffuse Unilateral Subacute Neuroretinitis)	Caused by motile subretinal nematode – Baylisascaris procyonis (raccoon roundworm) or Ankylostomum caninum (dog hookworm); Loss of central vision and transient obscurations	ERG is subnormal in early disease

Contd

Contd

Contd.

Vogt Koyanagi Harada (VKH) Syndrome

VKH typically affects **pigmented people**, MC **Japanese and Hispanics** in whom **HLA DR1 and HLA DR4** predominate.

Vogt Koyanagi: skin changes and anterior uveitis.

Harada disease: **neurological** features (meningitis, encephalopathy, tinnitus, vertigo, deafness, CSF lymphocytosis) and **exudative RD** predominate.

VKH Convalescent phase: localized **alopecia**, **poliosis** (whitening of hair), **vitiligo** **Sunset glow fundus** and depigmented limbal lesions (**Suglura sign**).

Uveal Effusion Syndrome

Idiopathic syndrome occurring in **hypermetropic and nanophthalmic** (extreme hypermetropic) eyes in middle aged men.

Structurally abnormal thick sclera containing excess proteoglycans that trap water and lead to accumulation of protein rich fluid in the supravveal space

Ciliochoroidal detachment and **exudative retinal detachment**

Following resolution of fluid retina may show **leopard spot mottling**

Uveal effusion / ciliochoroidal detachment is a/w: **Low IOP**; **Shallow anterior chamber**; **Brown smooth immobile elevations of choroids** NOT extending to posterior pole.

Acute Retinal Necrosis (ARN)

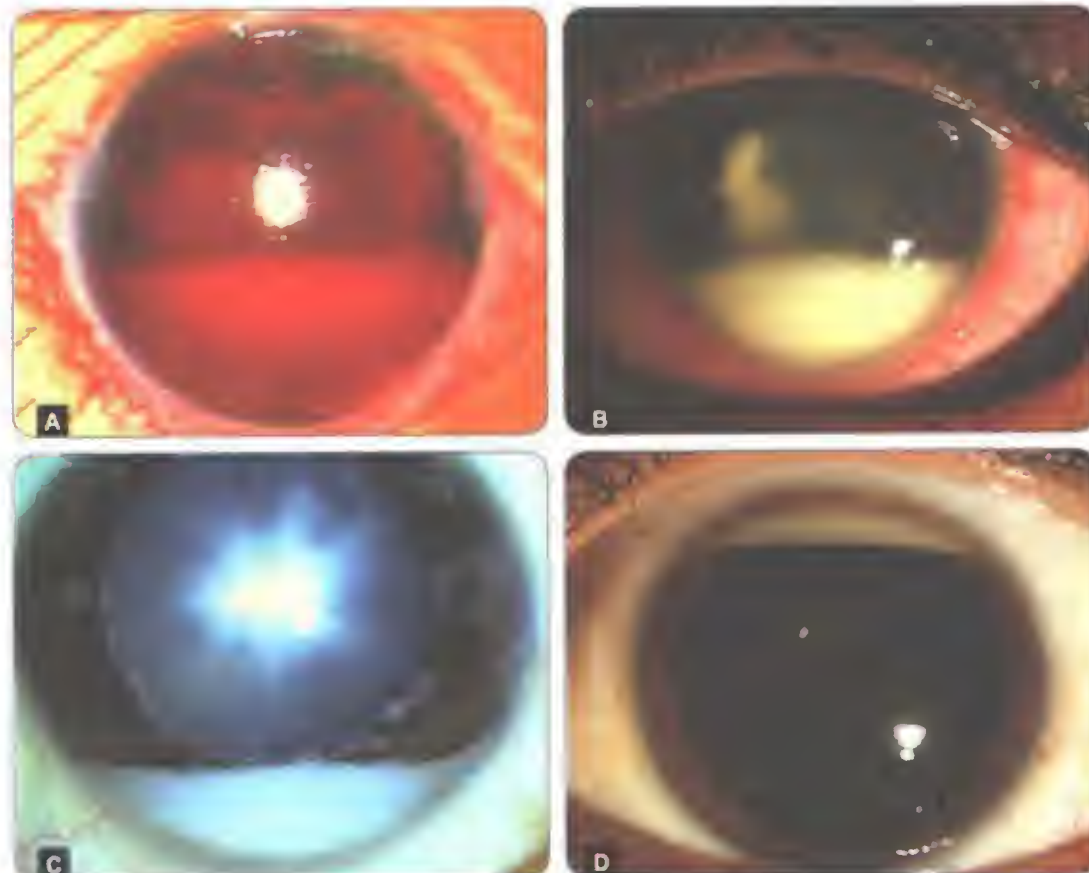
Caused by **Herpes simplex in young age** and **Herpes (varicella) zoster in old age**.

Arteritis, periphlebitis, necrotising retinitis; severe vitritis; **posterior pole is usually spared until late**.

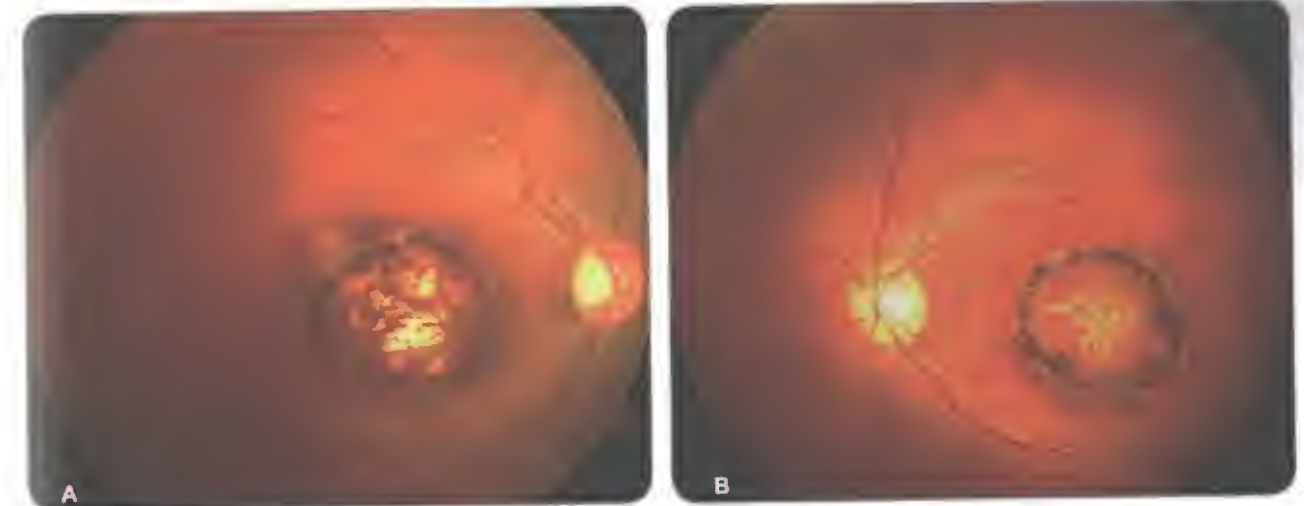
Presumed Ocular Histoplasmosis Syndrome (POHS)

Caused by **Histoplasma capsulatum**, disease acquired by **Inhalation**, so far Histoplasma capsulatum has NOT been recovered from an eye with POHS; disease MC in **Mississippi-Missouri river valley**.

Absence of intraocular inflammation
Atrophic "**hista**" spots,



Figs. 17.49A to D: Abnormal contents of anterior chamber. A. Hyphema-blood; B. Hypopyon-pus; C. Pseudohypopyon in retinoblastoma. D. Inverse hypopyon—emulsified silicone oil



Figs 17.50A and B: Bilateral congenital toxoplasmosis



Fig. 17.51: Cottage cheese and tomato ketchup retinopathy

Fig. 17.52: Headlight in the fog appearance

Sympathetic Ophthalmia

- **Etiology:**
 - Bilateral granulomatous uveitis occurring between 2 weeks to several years **after penetrating trauma to eye**.
 - Eye with penetrating injury/eye surgery is called 'exciting eye'. Fellow eye is called 'sympathizing eye'.
- **Clinically:**
 - **Earliest symptom** is **photophobia**; and **decreased accommodation** (blurring of near vision due to ciliary body involvement).
 - **Earliest sign** in the sympathizing eye is **retrolental cells/anterior vitreous cells**.
 - **Dalen fuchs** nodules are seen in histopathology.
- **Treatment:**
 - If the injured eye is unsalvageable, **enucleation** (**NOT evisceration**) should be done **within 2 weeks**.

Vitreous Hemorrhage

- MC cause of spontaneous vitreous hemorrhage in adults is **diabetic retinopathy**
- MC cause in **young** is **trauma**.
- Presents with **sudden or subacute unilateral painless decreased vision** a/w **floaters** and **absence of fundal glow** on ophthalmoscopy.
- **B-scan** helps in diagnosing and non-resolving hemorrhage requires **pars plana vitrectomy**.

Eales's Disease

- Eales disease is an **idiopathic, peripheral retinal vasculopathy** characterized by inflammation, ischemia, retinal neovascularization and is **hallmarked by recurrent vitreous hemorrhages**.
- Eales's disease has been reported predominantly in India

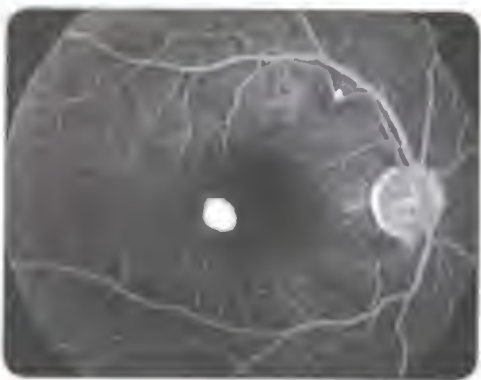


Fig. 17.56: ink blot appearance on FFA in central serous retinopathy

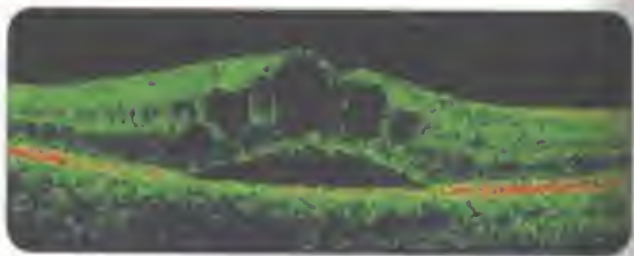


Fig. 17.57: OCT of cystoid macular edema

FUNDOSCOPY

Condition	Fundus
CRAO	Cattle trucking appearance
CRVO	Blood and thunder fundus
Hyper-metropia	Silk shot retina (pseudopapillitis / pseudoneuritis)
Sickle cell anemia	Sea fan retinopathy ('parachute lesions'). Rising sun appearance
Pars Planitis	Snowbanking
Sarcoidosis	Candle wax drippings, Lander's sign
Salt and Pepper fundus	Congenital syphilis Leber's amaurosis Congenital Rubella
Purtscher's retinopathy	Bilateral multiple cotton wool spots and/or superficial hemorrhages around optic nerve; By definition, seen in severe head and chest injury; "pseudo Purtscher's retinopathy" = embolism (fat, air, amniotic fluid), acute pancreatitis, SLE, lymphoma, TTP, after BMT
Uyemura's fundus	Xerophthalmic fundus
Mizuo phenomenon	Oguchi's disease (congenital stationary night blindness)
Angioid streaks	Orange peel or peau de orange appearance of retina
Terson syndrome	Intraocular hemorrhage (intra retinal and vitreous hemorrhage) + subarachnoid hemorrhage
Shaken Baby syndrome	Multilayered hemorrhages (pre, intra and sub-retinal) hemorrhages
Morning glory syndrome	Mesodermal defect with lamina cribrosa deficient
Sturge Weber syndrome	Tomato catsup fundus (Diffuse choroidal hemangioma)
Tuberous sclerosis	Mulberry tumor (retinal astrocytoma)
Best disease	Scrambled egg/Egg Yolk and pseudohypopyon maculopathy
End stage PORN	Cracked Mud appearance (Progressive Outer Retinal Necrosis)
Acute retinal necrosis	Swiss cheese pattern
CMV retinitis	Cottage cheese and tomato ketchup; pizza pie retinopathy
VKH syndrome	"Sunset Glow" fundus, chronic/recovery stage
Toxoplasmosis	"Headlight in fog" appearance - choroiditis seen through vitreous haze
Histo spots	yellow white punched out round spots usually < 1 mm deep to the retina in ocular histoplasmosis

Cotton Wool Spots (CWS)

- Acute obstruction of precapillary retinal arteriole causing blockage of axoplasmic flow and buildup of axoplasmic debris in the retinal nerve fibre layer - seen as cotton wool spot (CWS).
- Note: Even a single CWS is abnormal.
- DM is MC cause; Also seen in acute or chronic HTN; CRVO, BRVO; HIV retinopathy; collagen vascular disease (SLE - MC); Infections; Giant cell arteritis; Purtscher retinopathy; radiation retinopathy; interferon therapy; Cancers; Hypercoagulable states; Others (migraine, hypotension; IV drug abuse; papilledema, papillitis, sickle cell anemia, acute blood loss).

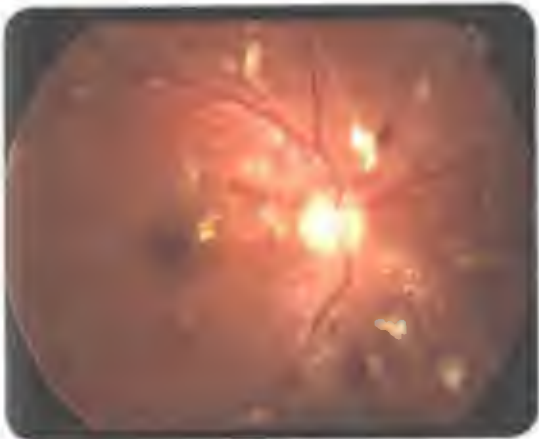


Fig. 17.58: Cotton wool spots (soft exudates) in the retina

DIABETIC RETINOPATHY (DR)

- Duration of diabetes is the most important determining factor. Longer duration of diabetes, more is the risk for DR.
- Good metabolic control of diabetes will NOT prevent DR, although it delays its development by a few years.
- Systemic factors which have an adverse effect on DR include—pregnancy; hypertension, renal disease, obesity, hyperlipidemia, smoking, anaemia.

Pathogenesis

- Microvascular occlusion
- Retinal hypoxia: → Neovascularization—hallmark of PDR
- Microvascular leakage: In DM, there is ↓↓ in the number of pericytes (breakdown of blood retinal barrier) → retinal edema, hard exudates, hemorrhage.
- Capillary distension and loss of pericytes → saccular pouches of the vessel wall (microaneurysms).

Classification of DR

Non-proliferative DR (NPDR)

- NPDR maybe mild, moderate or severe. Ophthalmoscopic features of NPDR include
- Microaneurysms in macular area (earliest clinically detectable lesion); they are located in inner nuclear layer
- Retinal hemorrhages, both superficial (flame shaped) and deep (dot blot hemorrhages).
- Hard exudates—yellowish white, waxy, patches arranged in clumps or in circinate pattern around macula (circinate retinopathy); they are located in outer plexiform layer.
- Retinal edema characterized by retinal thickening.
- Cotton wool spots (if >8, high risk of developing PDR).
- Venous abnormalities, beading, looping, dilation.
- Intraretinal microvascular abnormalities (IRMA).

Diabetic Maculopathy

- ▶ Focal, Diffuse, Ischaemic or Mixed
- ▶ Clinically significant macular edema (CSME)
 - Retinal edema within 500 μ of centre of fovea.
 - Hard exudates within 500 μ of centre of fovea + adjacent area of retinal thickening
 - Retinal edema > 1 disc diameter, any part of which lies within 1 DD of centre of fovea.

Proliferative DR (PDR)

- NVD (Neovascularization at disc)
- NVE (Neovascularization elsewhere)
- Preretinal haemorrhage
- Vitreous haemorrhage (VH)
- Tractional RD
- Neovascularization of iris and or angle.

Management of DR

Most accepted diabetic retinopathy study is ETDRS (Early Treatment Diabetic Retinopathy Study).

Diabetes Type	First Examination at	Follow-up at
Type 1	3-5 years after onset (in all patients > 9 years of age)	Yearly
Type 2	At time of diagnosis	Yearly
Prior to pregnancy or during pregnancy (type 1 or type 2)	Prior to conception or early in the first trimester	Every 3 months until delivery

Specific Treatment

- **Mild NPDR:** Periodic examination as outlined above.
- **Moderate to severe NPDR:** patient should be followed up very closely. However treatment (argon laser photocoagulation) is warranted in —unilateral patient, pregnancy, renal/cardiac failure, etc.
- **Diabetic maculopathy**
 - **Focal maculopathy:** focal argon laser photocoagulation required around the microaneurysms or leaking vessels.
 - **Diffuse maculopathy:** 'macular-grid' photocoagulation required, but avoid the fovea.
 - **Ischaemic maculopathy:** Photocoagulation will NOT improve vision.
- **PDR:** The treatment of choice is argon laser **Pan Retinal Photocoagulation (PRP)**.
- **Advanced PDR** with fibrotic bands, tractional retinal detachment and proliferative vitreoretinopathy - Vitrectomy with epiretinal membrane peeling with endo-photocoagulation and reattachment of detached retina.



Fig. 17.59: Hard exudates in circular pattern around macula called circinate retinopathy

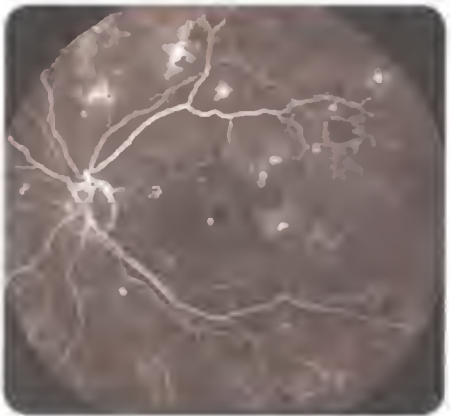


Fig. 17.60: Fluorescein angiogram of NPDR: The bright spots indicate leakage from microaneurysms; the darker areas are avascular areas

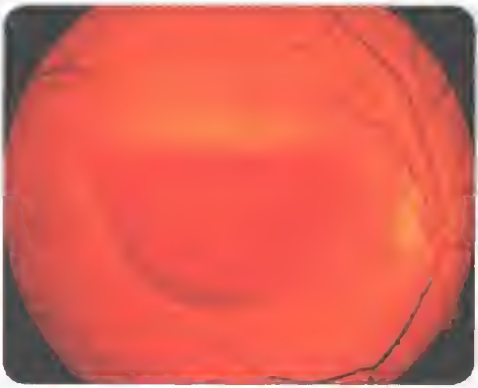


Fig. 17.61: Subhyaloid hemorrhage

Other Ocular Signs in Diabetes Mellitus

- **Visual Defects**
 - **Hyperglycemia** → increased refractive index of lens → **myopic** shift
 - **Hypoglycemia** → decreased refractive index of lens → **hypermetropic** shift.
 - **Diplopia** in ophthalmoplegia caused by neuropathy
- **Ocular Movements**
 - Sudden onset of muscle palsies (third nerve, sixth nerve), especially, **Pupil sparing third nerve palsy**.
- **LIDS**
 - **Xanthelasma** (due to associated hyperlipidemia).
- **Cornea**
 - **Delayed epithelial healing; Punctate keratopathy; wrinkling** of Descemet's membrane.
 - **Decreased corneal sensation** (due to trigeminal neuropathy).
- **IRIS**
 - **Hydrops** of pigment epithelium (due to transient glycogen storage), release of pigment into AC during surgery or simply even after dilation of pupil.
 - **Rubeosis iridis**.
- **Lens**
 - **Snowflake** cataract.
 - **Early onset** of senile cataract.
- **VITREOUS**
 - **Vitreous haemorrhage (Diabetes is MC cause of VH in adults)**
- **RETINA**
 - Diabetic retinopathy (as discussed already).
 - **CRVO**.
 - **Lipemia retinalis** (due to associated triglyceridemia, in keto-acidosis).
- **IOP**
 - Increased incidence of **POAG**.
 - **Neovascular glaucoma**.
 - **IOP decreased in diabetic ketoacidosis** (due to increased plasma bicarbonate level).

RETINAL VESSEL OCCLUSIONS

Central Retinal Artery Occlusion (CRAO)

- **Embolism** from carotid atherosclerosis is MC cause of CRAO.
- **Amaurosis fugax** (transient sudden visual loss lasting for few minutes due to occlusion by minute emboli) may be premonitory. **Sudden painless loss of vision, RAPD, white retina, cherry red spot in macula, attenuated retinal arterioles**, sludging of blood in the vessels called as "**cattle trucking (boxcarring) appearance**" and Hollenhorst plaque. After a week, the retina resumes its normal appearance leaving behind **atrophic white optic disc and thread like retinal arteries**.
- **Susac syndrome:** triad of CRAO, sensorineural deafness, encephalopathy.
- **Treatment:** lie flat, **ocular digital massage** for 15 minutes (to dislodge emboli, lower IOP), **anterior chamber paracentesis, IV acetazolamide/mannitol; hyperbaric oxygen**.

Variants of CRAO

- **Branch Retinal Artery Occlusion:** BRAO follows lodgement of cholesterol embolus at arteriolar bifurcation (**Hollenhorst plaque**); **altitudinal visual field defect**.
- **Cilioretinal artery occlusion:** Cilioretinal artery perfuses retina but is **derived from posterior ciliary circulation**, present in 30% of individuals; here **pallor is localized to posterior pole**.
- **Ophthalmic artery occlusion:** Total afferent pupillary defect; PL negative); Intense retinal whitening (both retinal and choroidal circulation are simultaneously involved).



Fig. 17.62: Cherry red spot at macula



Fig. 17.63: Macular hole formation

Causes of Cherry Red Spot

Ocular Causes
Central Retinal Artery Occlusion (CRAO) Berlin's edema of the macula (commotio retinae) Macular hole with surrounding retinal detachment Quinine toxicity Ocular ischemic Syndrome
Others
Infantile Metachromatic Leukodystrophy Goldberg's syndrome Hurler's syndrome B-galactosidase deficiency Hallevorden Spatz disease
Lysosomal Storage Disorders (Sphingolipidoses)
Tay-Sach's disease (MC metabolic cause) Niemann Pick's disease (less common than in Tay Sach's) Sandhoff's disease (GM2 gangliosidosis type 2) Generalized GM1 gangliosidosis type 1 Sialodosis types 1,2 (Cherry red spot-myoclonus syndrome) Farber's disease Batten Mayou disease ?? Gaucher's disease ??

EXTRA EDGE

- **Goucher's disease** is NOT COMMONLY GIVEN as a cause of cherry red spot in standard textbooks of medicine and ophthalmology except in Duker-Yanoff's Ophthalmology book – best option to choose if the question says – "cherry red spot is seen in all except"

Retinal Vein Occlusion (RVO)

- **Predisposing factors:**
 - **Systemic:** Increasing age (60s-70s); systemic hypertension and diabetes mellitus; hyperviscosity syndromes; hyper-homocysteinemia.

- ▶ **Ocular: Raised IOP (POAG)**, hypermetropia, head trauma, optic disc drusen, congenital anomaly of the CRV.
- **Mechanism:** The vein is compressed by a thickened artery where the two share a common adventitia (i.e. at A-V crossings in the retina and just behind the lamina cribrosa).

Central Retinal Vein Occlusion (CRVO)

Non-Ischaemic CRVO	Ischaemic
More common (75% of cases)	Less common
Moderate loss of VA	Severe loss of VA (< 6/60 or worse)
Slight RAPD (Marcus Gunn pupil)	Marked RAPD
Mild tortuosity and dilation of all branches of the CRV	Marked tortuosity and engorgement of retinal veins
Mild to moderate retinal haemorrhages (dot-blot and flame shaped) in all 4 quadrants and most numerous in the periphery	Extensive retinal haemorrhages involving both peripheral retina and posterior pole (Blood and Thunder fundus)
Few cotton wool spots	Numerous cotton wool spots
Mild optic disc edema and macular edema	Severe optic disc edema and hyperemia
FFA: venous stasis but good retinal capillary perfusion	FFA: masking of retinal vascular bed by retinal haemorrhages and extensive areas of capillary non-perfusion
Prognosis: Good return of VA to near normal in 50% of patients. Main cause for persistent poor VA is chronic cystoid macular edema	Prognosis: VA is permanently impaired due to macular ischaemia. Rubeosis iridis develops in about 50% of eyes at 3 months (the "100 day glaucoma"), neovascular glaucoma, vitreous haemorrhage, ERG is subnormal (reduced b/a ratio)
Treatment: Treat predisposing factor	Treatment: PRP (or cryoapplication if media is hazy)

EXTRA EDGE

- Feature favoring **Ocular Ischemic syndrome** (instead of CRVO) are ; delayed choroidal filling, arterial pulsations with slight pressure; bilaterality (in 20%) and retinal artery pressure is **low** (by ophthalmodynamometry); ALSO symptoms (**pain, loss of vision**) are **more** compared to signs in OIS and in OIS patient may complain of **persistent after images** and worsening of vision with exposure to bright light ("bright light amaurosis fugax) with slow adaptation

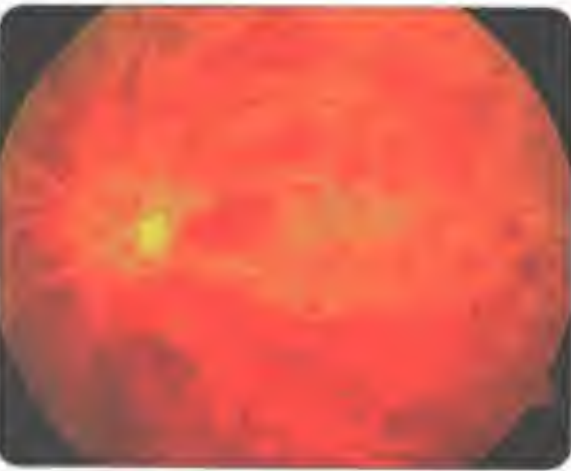


Fig. 17.64: Blood and thunder fundus in ischemic CRVO

Branch Retinal Vein Occlusion (BRVO)

- **Three times more common than CRVO.**
- Clinical features: **Sudden onset of blurred vision and metamorphopsia** or a relative visual field defect;
- Complications: Neovascularization, **Chronic macular edema** (MC cause of persistent poor VA after BRVO)
- Treatment: Wait 8-12 weeks for retinal haemorrhages to clear and spontaneous visual improvement to occur. If VA continues to be 6/12 or worse after 3 months, Argon laser photocoagulation should be considered.



Fig. 17.65: Branch retinal venous occlusion

EXTRA EDGE

- Recent advances**
 - Ozurdex is a **dexamethasone intravitreal implant (0.7 mg)** approved for treatment of
 - 1. Macular edema following CRVO or BRVO
 - 2. Noninfectious posterior uveitis
 - It is in a biodegradable polymer form and slowly releases the drug over a 6 months period.
 - See under **anti-VEGFs in Ophthalmology** below for more about Intravitreal Avastin.

RETINAL DETACHMENT (RD)

Definitions

- RD is separation of the neurosensory retina from the retinal pigment epithelium (RPE), (which represent the two layers of the primary optic vesicle), by subretinal fluid (SRF).
- ▶ **Retinoschisis:** is the splitting of the sensory retina into two layers.
- ▶ **Retinal break:** is a full thickness defect or discontinuity in the sensory retina.
- ▶ **Tears** are caused by dynamic vitreoretinal traction; they have a predilection for the upper temporal fundus, more dangerous than hole.
- ▶ **Holes:** are caused by chronic atrophy of the sensory retina; they have a predilection for the upper temporal fundus; less dangerous than tears.
- ▶ **Primary break** is defined as the one responsible for the RD.
- ▶ **Secondary break** is not responsible for the RD or forms after RD has occurred.
- ▶ The **upper temporal quadrant** is the MC site for retinal break formation.
- **Synechesis:** is the contraction of vitreous gel that separates from solid components.
- **Synchisis:** is the liquefaction of vitreous gel.
- **Choroidal detachment:** is an effusion into the suprachoroidal space (a/w hypotony).
- Clinically RD is best diagnosed by **Indirect Ophthalmoscopy of dilated fundus**.

Peripheral Retinal Degenerations

- Degenerations Predisposing for RD**
 - **Lattice degeneration**—MC retinal degeneration leading to RD; important cause of RD in **young myopes**; MC in **upper temporal** peripheral fundus; lattices also seen in **Marfan's syndrome**; **Ehler Danlos syndrome**.
 - **Atypical lattice:** Is characterized by radial lesions, which appear continuous with the peripheral blood vessels; seen in **Stickler syndrome**.

- **Snail track degeneration**
- **White with pressure**; **White without pressure**
- **Focal pigment clumps**
- Benign degenerations:** Pavingstone degeneration; Snowflake; Peripheral (micro cystoid) degeneration.

Rhegmatogenous RD

- **MC type:** Due to **tear/break** in retina.
- **MC in myopes** due to frequent **lattice degeneration**.
- **Photopsia/flashes** (more temporally) and **floaters** present.
- Loss of vision like a "curtain coming across field of vision".
- **Schaffer's sign** - "**Tabacca dust**" in vitreous (anterior vitreous pigments)
- **Subretinal fluid extends upto ora serrata.**
- Features of **Chronic RD** = pigmented **demarcation line** (high **watermarks/tidemarks**); intraretinal cysts, fixed folds, white dots underneath the retina (subretinal precipitates), relative visual field defect.
- Treatment: **laser photocoagulation**; **cryotherapy**; **pneumatic retinopexy**; **vitrectomy**, **scleral buckling (encercilage)** or a combination of these with endolaser photocoagulation

Tractional RD

- (2nd MC type) Due to **proliferative vitreoretinopathy** – sensory retina is **pulled** away from the RPE by contracting vitreoretinal membranes; the source of SRF is unknown; **MC in diabetics**

Exudative RD

- NO tear/break; SRF **derived from the choroids** gains access to subretinal space through damaged RPE
- Causes are – **choroidal melanoma**, **toxemia of pregnancy**, **malignant hypertension**, **Harada's disease**.
- NO photopsiae/floaters
- **Shifting of subretinal fluid** is the hallmark
- D/D of Bilateral Exudative RD
 - Ca metastasis to choroid, Uveal effusion syndrome, Posterior scleritis, Eclampsia, Central serous retinopathy, Wet ARMD

EXTRA EDGE

- **Ocriplasmin** is a **recombinant protease** has been FDA approved for treatment of symptomatic **vitreomacular adhesion**.



Fig. 17.66: Rhegmatogenous RD large horseshoe tear in the retina

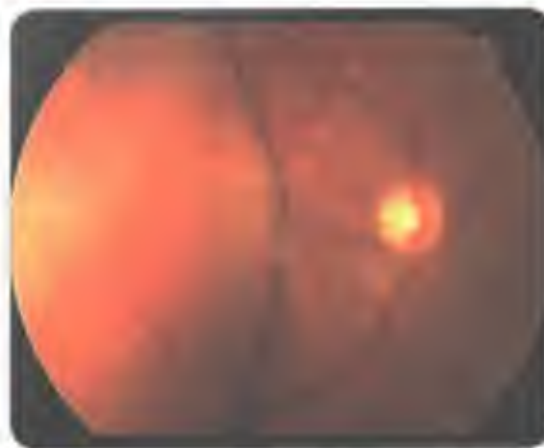


Fig. 17.67: Exudative retinal detachment

Agents for Retinal Tamponade

- Retinal tamponade is used in retinal detachment treatment and aims to ensure adhesion of the detached neurosensory retina to the retinal pigment epithelium.
- Agents used for retinal tamponade (vitreous substitutes) are
 - Gases: **SF₆** (sulfur hexafluoride); **C₃F₈** (perfluoropropane); **C₂F₆** (perfluoroethane); **air**
 - Oil: **Silicone oil**
 - Liquid: **PFCL** (Perfluorocarbon liquid).

RETINITIS PIGMENTOSA (RP)

- Typical RP is a diffuse **bilaterally symmetrical** retinal dystrophy **predominantly affecting rods**.
- Inheritance: Sporadic; **AR (MC)** > **AD** (best prognosis) > **XLR** (least common, worst prognosis), or digenic inheritance also; female carriers have normal fundi or show 'golden-metallic' **tapetal reflex** temporal to the macula.
- Clinical features:
 - Defective dark adaptation (night blindness, **nyctalopia**), progressive visual field defect.
 - Classic triad of RP: (1) **arteriolar attenuation** (2) **bone-spicule pigmentation** that is perivascular and more in equatorial region (3) **Waxy pallor of optic disc** that is **least reliable sign** of the triad.
 - Unmasking of larger choroidal vessels (due to pigment migration) gives the fundus a **tessellated appearance**.
 - Three types of **maculopathy** that may be seen are—**atrophic**, **cellophane**, **cystoid macular edema**.
 - Associated ocular features: optic disc drusen, open-angle glaucoma, **posterior subcapsular cataracts**, **keratoconus**, **myopia**, **posterior vitreous detachment**.

RP like fundus picture is seen in

- End stage chloroquine retinopathy
- End stage syphilitic retinopathy
- Cancer related retinopathy
- Investigations:
 - ERG**—reduced amplitude of scotopic and photopic b-wave, delay in time between the flash of light and peak of b-wave (**delayed implicit time**; **ERG slows appear before** clinical symptoms and signs appear)
 - EOG**—absence of light rise.
 - Visual field: initially **annular/ring** scotoma (**structural retinal changes start at mid periphery and later spread towards the posterior pole/centre**), later progressive constriction of visual field.
- Atypical RP
 - Retinitis punctata albescens**.
 - Sector RP**: involves of only one quadrant (usually nasal) or one half (usually inferior); many cases remain stationary.
 - Pericentric RP**.
 - RP with exudative vasculopathy** (Coats disease-like telangiectasias)

EXTRA EDGE

- Epiretinal and subretinal microchip implants** have been used with modest success in RP - still in research.

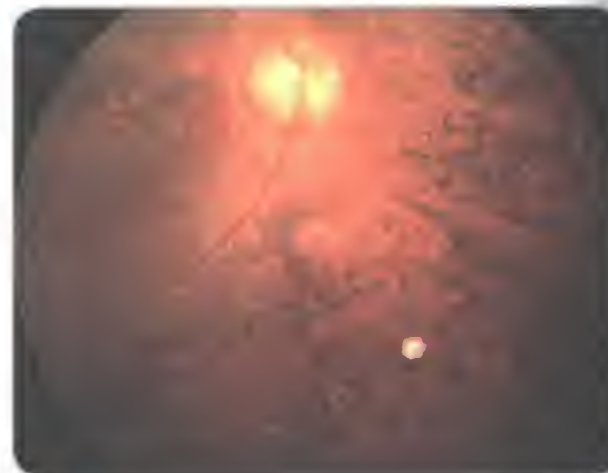


Fig. 17.68: Retinitis pigmentosa

Syndromes A/W Retinitis Pigmentosa

- All are autosomal recessive.
- Bassen-Kornzweig syndrome (Abetalipoproteinemia)** **Acanthocytosis**, fat malabsorption, ataxia; **jejunal biopsy is diagnostic**

Syndromes A/W Retinitis Pigmentosa

- Refsum's syndrome**: Due to defective metabolism of **phytanic acid that accumulates**. Peripheral neuropathy, cerebellar ataxia, elevated CSF proteins, deafness, ichthyosis, cardiac arrhythmias
- Bardet-Biedl syndrome**: **Mental retardation, polydactyly, obesity, hypogonadism**; (coned rod dystrophy causing Bulls eye maculopathy is typically a/w Bardet Biedl syndrome)
- Usher's syndrome**: Sensorineural deafness.
- Kearns-Sayre syndrome**: Chronic progressive external ophthalmoplegia, heart block.
- Cockayne's syndrome**: **Bird-like facies**, dwarfism, flexion contracture of limbs, mental retardation, ataxia and premature aging.
- Cohen syndrome**: Facial dysmorphism, prominent incisors, mental deficit, muscle hypotonia, truncal obesity
- Friedrich ataxia**: Ataxia, nystagmus
- HARP syndrome** - a.k.a. Hallervorden-Spatz disease: Hypoprebetalipoproteinemia, acanthocytosis, RP, Pallidal degeneration (Progressive extrapyramidal dysfunction and dementia)
- NARP syndrome**: Neuropathy, Ataxia, RP

Ring Scotoma Seen in

- Retinitis pigmentosa

Types of ARMD

Non-exudative (Dry, Atrophic) ARMD	Exudative (wet, neovascular) ARMD
<ul style="list-style-type: none"> MC type—90% of cases; causes mild to moderate gradual loss of vision over many years. Clinically appears as sharp circumscribed areas of RPE atrophy with varying degrees of loss of choriocapillaries. Treatment: No effective treatment except for provision of low visual aids. Antioxidants: as per AREDS study (Age Related Eye Disease Study) vitamin C, beta carotene, zinc, cupric oxide is useful. 	<ul style="list-style-type: none"> Less common, but a/w rapidly progressive loss of vision, all central vision may be lost within a few weeks. Two important features of exudative ARMD are detachment of the RPE and choroidal neovascularization (subretinal or choroidal neovascular membranes, SRNVM or CNVM); Disciform scarring at the macula Treatment: Argon laser photocoagulation For newer treatments see below.

ANTI-VEGFs IN OPHTHALMOLOGY

- Vascular Endothelial Growth Factor (VEGF) **promotes angiogenesis**, increases vascular permeability and has proinflammatory action.
- In the human eye, **increased levels of VEGF correlate with retinal ischemia associated neovascularization** in diabetic retinopathy, retinal venous occlusion and retinopathy of prematurity; also VEGF levels are elevated in wet AMD.
- Hence anti-VEGF agents are developed to use in these conditions; all are used **intravitreally**.

- High Myopia
- Aphakic spectacle correction
- Pan retinal Photocoagulation

Tubular Vision Seen in

- Advanced Retinitis pigmentosa
- High myopia
- Central retinal artery occlusion with sparing of cilio-retinal artery.
- Advanced Glaucoma

AGE-RELATED MACULAR DEGENERATION (ARMD)

- A bilateral disease that is a **leading cause of blindness in the western world**.
- Drusen**
 - Earliest clinically detectable feature of ARMD are drusen, which are, yellow-white spots at the posterior pole.
 - Drusen consist of focal aggregations of hyaline material located between the basal lamina of the RPE and inner collagenous layer of Bruch's membrane.
 - Drusen may be hard, soft, diffuse, or calcified.

Currently Available Anti-VEGFs are

Pegaptanib sodium (Macugen)	First FDA approved anti-VEGF; it is a pegylated aptamer which binds with high affinity to the major pathologic VEGF isoform, VEGF165 thereby inhibiting it from binding to its receptor;
Bevacizumab (Avastin)	Humanised monoclonal antibody against VEGF; currently FDA approved for IV treatment of colorectal cancer ; ocular uses are off-label but found safe and effective worldwide.
Ranibizumab (Lucentis)	Second FDA approved anti-VEGF; Humanised monoclonal antibody against VEGF
Aflibercept (eyelea)	Anti-VEGF fusion protein that binds all isoforms of VEGF-A and placental growth factor

Indications of Anti-VEGFs

- **Wet ARMD** (choroidal neovascular membrane, CNVM)
- **Diabetic retinopathy** (for macular edema)
- **Retinal Venous occlusive disease** (for macular edema)

Other Angiostatic Drugs

Anecortave Acetate
(Retaane)

An **angiostatic cortisone** which lacks glucocorticoid activity (hence ocular hypertension and cataracts are avoided); Used for **wet AMD (CNVM)**.

Squalamine lactate
(Evlzon)

Systemically administered anti angiogenic compound; was **discontinued** since it was not better than ranibizumab.

Photodynamic Therapy (PDT)

- **Photodynamic therapy** is used in the treatment of **wet ARMD**. **Verteporfin** dye and **diode laser** is used. *Less popular now* due to availability and efficacy of anti-VEGFs.

Choroidal Neovascular Membrane

- Grey-green membrane or blood seen deep to retina.
- **More common causes:** **ARMD**, **high myopia**, **IPCV** (**idiopathic polypoidal choroidal vasculopathy**), **angioid streaks**, **choroidal rupture (trauma)**, ocular histoplasmosis.

OTHER RETINAL DISORDERS

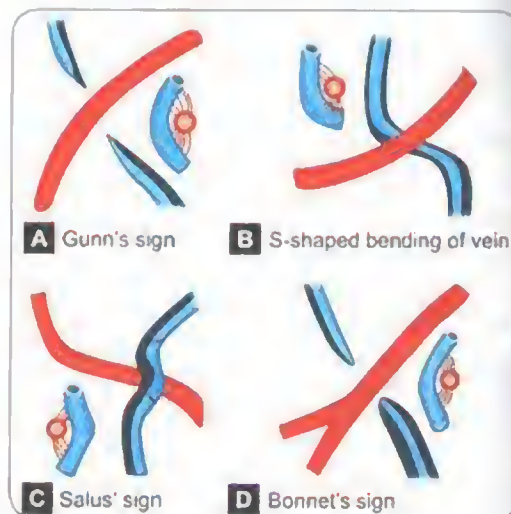
Hypertensive Retinopathy

The fundus picture of hypertensive retinopathy is characterized by:

1. **Vasoconstriction** → generalized and focal **arteriolar narrowing**; obstruction of precapillary arterioles → **cotton wool spots**. (reflects **severity of HTN**)
2. **Leakage**—caused by abnormal vascular permeability → **flame shaped haemorrhages**, **hard exudates** and **retinal edema**. Hard exudates around the fovea in Henle's layer → **macular star**.
3. **Arteriosclerosis** → thickening of vessel wall → clinically seen is the presence of marked changes at AV crossings (**AV nipping** which also indicates that hypertension has been present for a **long time** - reflects **duration of HTN**)

Grading of Hypertensive Retinopathy (Keith Wagner Barker Grading)

- Grade I—mild generalized **arteriolar attenuation with broadening of arteriolar light reflex** and concealment.
- Grade II—more severe generalized and focal arteriolar constriction associated with deflection of veins at crossings (**Salus' sign**).
- Grade III—'copper-wiring' of arterioles, banking of veins distal to AV crossings (**Bonnet sign**), tapering of veins on either side of crossings (**Gunn sign**). Flame shaped haemorrhages, cotton wool spots, and hard exudates also present.
- Grade IV—all **grade 3 changes** + '**silver wiring**' + **dissecting intraretinal haemorrhages** + **macular star** + **renal insufficiency**.



Figs 17.69A to D: Arteriovenous crossing changes in hypertensive retinopathy

Hypertensive Choroidopathy

Rare, but may occur as a result of acute HTN crisis (accelerated HTN) in young adults.

- **Elshnig's spots:** Small black spots surrounded by yellow halo - represent choroidal infarcts.
- **Siegrist streaks** - flecks arranged linearly along choroidal vessels - indicates fibrinoid necrosis
- **Exudative RD** - sometimes bilateral - occurs in toxemia of pregnancy.

Central Serous Retinopathy

- Localized serous detachment of retina at macula due to RPE pump failure

Affects **young males** with **type A personality**, hypertensives, aggravated by **systemic steroid** usage; may be a/w **myopic disc pit**

Moderately blurred vision correctable with weak plus lens (**acquired hypermetropia**), **central positive scotoma** ('something blocking vision'), **micropsia**, **ring reflex** at macula, foveal reflex absent or distorted. Diagnosed by **fluorescein angiogram** - shows **smoke-stack pattern** more commonly (also called **mushroom** or **umbrella configuration**) or **ink-blot pattern**.

Usually **resolves spontaneously** in 80-90% cases.

Treat by **Argon Laser photocoagulation** if Long-standing (**>4 months**); If a/w with marked loss of vision; if recurrent CSR; If vision in fellow eye is permanently reduced due to previous attacks of CSR.



Fig. 17.70: Central serous retinopathy



Fig. 17.71: OCT central serous retinopathy

Retinopathy of Prematurity (RoP)

- **Pathogenesis:** **Upper temporal quadrant** of retina is the **last to develop vascularization** by full term; in prematures these vessels get occluded by high oxygen concentration; on return to normal atmospheric air, there is intense neovascularization at the border of these ischemic areas.

- Clinically detected by leukocoria (secondary to retinal detachment) and strabismus.
- Signs: Temporal dragging of macula/disc, tractional RD, myopia, strabismus, amblyopia.
- **International Classification of ROP (ICROP):**
 - Stage 1: demarcation line (between vascularized and non-vascularized) retina
 - Stage 2: ridge (demarcation line with elevation)
 - Stage 3: ridge + extraretinal fibrovascular proliferation.
 - Stage 4a: Partial retinal detachment not involving fovea
 - Stage 4b: Partial retinal detachment involving fovea
 - Stage 5: Total retinal detachment
 - **Plus disease:** arteriolar tortuosity and venous engorgement of the posterior poles
 - **Pre-plus disease** Abnormal-appearing vasculature that does not make criteria for Plus disease
 - **Aggressive posterior ROP (AP-ROP)** is a severe form of ROP that rapidly causes total retinal detachment without going through the normal stages of ROP; also called **type II ROP** or "**Rush**" disease.
- **Treatment:** **Laser photocoagulation** is the **preferred treatment** of choice. If laser is not available, **cryotherapy** may be performed; Laser photocoagulation is performed when ROP reaches type 1 pre-threshold disease.
- **Surgical treatment** is currently recommended for the following:
 - Zone I ROP: any stage with plus disease
 - Zone I ROP: stage 3 - no plus disease
 - Zone II ROP: stage 2 or 3 with plus
 - The number of clock hours of disease is no longer the determining factor
 - Eyes meeting these criteria should be treated within 72 hours.
- **Screening:** AAO (American Academy Ophthalmology) guidelines for screening ROP is given below:
 - Infants with a birth weight of less than 1500 grams or with a gestational age of 28 weeks or less, as well as selected infants between 1500 and 2000 grams with an unstable clinical course who are believed to be at high risk by their neonatologist.
 - The first examination should be performed between 4 and 6 weeks of chronological age OR alternatively within the 31st to 33rd week of postconceptual or postmenstrual age (gestational age at both PLUS chronological age) - For babies born between 27-30 weeks of gestational age, the initial examination will be **4 weeks after birth**.

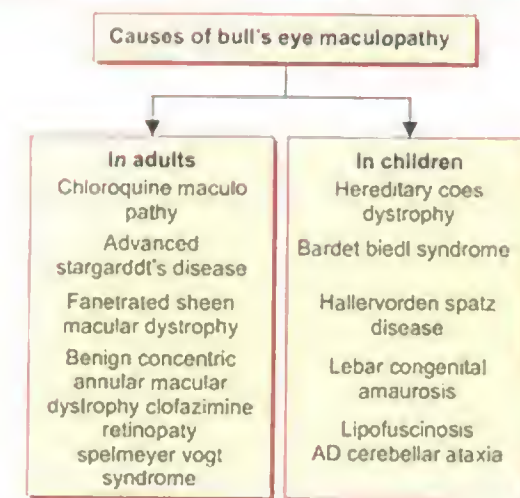


Fig. 17.72: Bull's eye maculopathy

Persistent Hyperplastic Primary Vitreous

- Early In embryonic life the lens is surrounded by embryonic vascular tissue (tunica vasculosa lentis), which in turn merges with the primary vitreous containing fibrovascular mesodermal tissue
- PHPV is usually **unilateral**
- Regression of this tissue may fail leaving **proliferating fibrovascular remnants**, either—
- 1. **Behind the lens (anterior PHPV)**: Mild remnant is **Mittendorf dot** appears as a small white axial nodule; more severe variants is **retrolental fibroplasia** with ciliary processes pulled centripetally; also a/w microphthalmia; ultimately **angle closure glaucoma** ensues.
- 2. **On the inner surface of the peripapillary retina (Posterior PHPV)**: It represents **persistent hyaloid vasculature on the optic disc**; **Bergmeister's papilla** is an isolated white mass containing hyaloid artery remnants on the optic disc; also a/w **Optic nerve hypoplasia**

may be seen; **Epiretinal membranes**, **falciform tractional retinal detachment**.

Idiopathic Polypoidal Choroidal Vasculopathy (IPCV)

- A.k.a **Posterior neal bleeding syndrome**; MC in **African females** and in **HTN** patients.
- **Subretinal red-orange polyp-like lesions** of choroidal vasculature.
- **ICG angiography**, may confirm the vessels arising from inner choroidal circulation with terminal aneurysmal dilatations (**popcorn lesions**).

Leber's Congenital Amaurosis

- **AR**; MC genetic cause of congenital blindness **African** in children.
- Fundus - pigmentary retinopathy; vision loss within few months of birth, infantile nystagmus, photophobia, **paradoxical pupillary response**, **oculodigital sign** (eye poking) and **flat ERG**; A/w **keratoconus**.
- **Gene therapy** targeting **RPE65 gene** has shown success in human trials.

Causes of Night Blindness (Nyctalopia)

1. Retinitis pigmentosa
2. **Gyrate atrophy of choroid**: first decade of life; **high plasma ornithine** levels; **lysine** is decreased; **scalloped RPE** and **choriocapillaris** in the retina; **constriction of visual fields** and **nonrecordable ERG**. **AR**. **Arginine restricted diet** needed; supplemental vitamin B6 (pyridoxine).
3. **Choroideremia**: **XLR**; affects **males** in first decade of life; loss of peripheral vision early; reduced ERG.
4. **Vitamin A deficiency**: **Uyemura's fundus**; small yellow white well demarcated spots deep in the retina.
5. **Zinc deficiency**: abnormal dark adaptation; zinc needed for vitamin A metabolism.
6. **Congenital Stationary Night Blindness (CSNB)**: Night blindness from birth, normal visual fields, not progressive; one variant is **Oguchi disease** in which **Mizuo phenomenon** occurs (fundus has a tapetum appearance in light adapted state but appears normally colored when dark adapted - takes about 12 hours).
7. **Undercorrected myopia**.

EXTRA EDGE

- **Cone dystrophy** causes **photophobia** and **vision worse during daytime (hemeralopia)** rather than night; also a/w **subnormal ERG**.

Electroretinogram (ERG)

- **a' wave** = photoreceptor (rods and cones) activity;
- **b' wave** = response of bipolar cells;
- **V' wave** = generated by retinal pigment epithelium and related to retinal metabolism.
- **Normal ERG** is biphasic.
- **Flat ERG**: advanced RP, CRAO, complete old RD, advanced glaucoma.
- **Subnormal ERG**: early RP, large area of retina is not functioning.
- **Negative ERG**: Gross disturbances of retinal circulation.
- **Pattern ERG**: Indicates activity of central macular region.
- **Multifocal ERG**: for disorders of central retina/fovea. It assesses **macular cone function**.

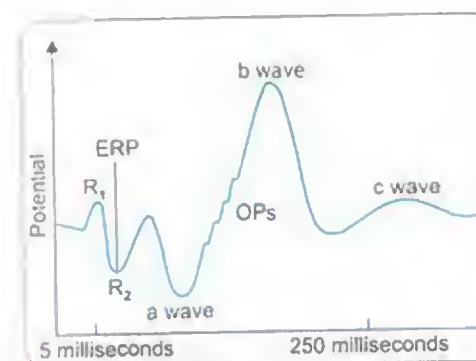


Fig. 17.73: Electroretinography

LACRIMAL DISORDERS

Probing and Irrigation Test

- Local anesthetic drops instilled, punctum dilated. Lacrimal cannula with saline filled syringe is passed into the lower punctum and advanced.

Hard Stop

- Occurs if the cannula enters the lacrimal sac but comes to a stop at the medial wall of the sac.
- This excludes complete obstruction of canalicular system.
- Then examiner irrigates - if saline passes into the nose, the patient has a patent lacrimal system.
- Failure of saline to reach nose indicates NLD obstruction here the lacrimal sac becomes distended and saline regurgitates through upper punctum.

Soft Stop

- If the cannula tops at or proximal to the junction of common canaliculus and lacrimal sac, i.e. at lateral wall of the sac.

Electroculogram (EOG)

- Reflects the activity of the **retinal pigment epithelium** and photoreceptors
- Measures the standing potential between the electrically positive cornea and the electrically negative back of the eye; Performed in both light and dark adapted states
- **Arden ratio** = **light peak/dark trough** = **1.85 or 185%** (Normal value).
- **Subnormal EOG** is confirmatory in **Best disease** (AD); ERG is normal

- The sac is thus NOT entered. Irrigation will therefore NOT cause the sac to distend.
- If lower canaliculus is blocked saline will regurgitate through lower punctum; if common canaliculus is blocked saline will regurgitate through upper punctum.

Jones Dye Testing

- ONLY indicated in subjects with partial obstruction of the lacrimal system. These patient manifest epiphora but lacrimal system can be successfully irrigated. Dye test is of NO value in total obstruction.
- **Primary test**: differentiates partial obstruction of lacrimal passages from hypersecretion of tears.
 - A drop of fluorescein is instilled in conjunctival sac and after 5 minutes a cotton bud moistened with local anesthetic is inserted under the inferior turbinate at the NLD opening. Results are:
 - **Positive**: fluorescein recovered from the nose indicates patency of drainage system; epiphora is due to hypersecretion only.
 - **Negative**: no fluorescein on cotton bud in nose indicates partial obstruction or failure of lacrimal pump mechanism; so move on to part 2 of this test.
- **Secondary (Irrigation) test**: indicates probable site of obstruction.

Dacryocystitis

- **Acute dacryocystitis**
 - Inflammation of lacrimal sac a/w nasolacrimal duct (NLD) obstruction.
 - **Streptococcus pneumoniae** MC.
 - Severe pain, redness, watering, purulent discharge, tender swollen lacrimal sac (usually **below medial palpebral ligament**).

➤ Treatment: Oral and topical *antibiotics*, NSAID's. Once acute condition resolves, *dacryocystorhinotomy (DCR)* is definitive treatment.

• Chronic dacryocystitis

➤ Watery, minimal inflammation, chronic, recurrent conjunctivitis

➤ Treatment: *DCR*

• Congenital dacryocystitis

➤ Due to failure of opening of NLD into the inferior meatus of nose, which normally occurs by 3rd week of life. Constant watering and regurgitation of pus through punctal.

➤ Treatment: *hydrostatic massage with antibiotic drops till 6 months of age.*

➤ *Probing with syringing at 10–12 months of age*; if it fails repeat after 4 weeks.

➤ *DCR only after 4 years of age.*

Dacryocystorhinostomy (DCR)

➤ A communication is made between the *lacrimal sac* and *middle meatus* of nose.

➤ *External DCR is gold standard*; can also be done endonasally and with laser probe. Introduced through lacrimal punctum; *Endolaser DCR* (ostium made endoscopically with Holmium YAG or KTP laser – low success -70%).



Fig. 17.74: Acute dacryocystitis

• Dacryoadenitis

➤ *Unilateral* lacrimal gland inflammation; swelling in temporal aspect of upper eyelid, *S-shaped ptosis*, tender lacrimal gland.

➤ MC ocular manifestation of *mumps* is *dacryoadenitis*.

➤ Treatment: Oral antibiotics, NSAIDs.

• Chronic canaliculitis

➤ By *Actinomyces israelii*; treat with antibiotic drops and *canaliculotomy*.

BLUNT OCULAR TRAUMA

• Also called *concussion* or *contusion injuries*. Can occur due to *blow by a fist, tennis ball or shuttlecock* etc... striking the eye.

• Various damages to eye structures occurring due to blunt trauma are as below:

Ocular tissue involved	Clinical manifestations
Orbit	<i>Blow out</i> fracture of <i>floor (MC)</i> or medial wall. Orbital hematoma Carotid Cavernous fistula
Eyelids	Hematoma Avulsion of lower lid
Conjunctiva	Subconjunctival hemorrhage
Anterior uvea	Hyphema (<i>"8"ball</i> or <i>'black ball'</i> hyphema = total hyphema with deoxygenated blood – refers to 8/ball of snooker game!) Iris sphincter tears and <i>iridodialysis</i> (<i>Ir shaped pupil</i>) <i>Angle recession</i> (can lead to glaucoma) and <i>cyclodialysis (hypotony)</i> Traumatic mydriasis Traumatic iritis
Lens	<i>Rosette</i> cataract <i>Vossius ring</i> (impression of <i>mlotic pupil</i> striking lens) Subluxation of lens
Sclera	Rupture, commonly at limbus or behind insertion of recti (<i>sclera thinnest behind recti insertion</i>)
Vitreous	Hemorrhage
Choroid	Choroidal rupture Suprachoroidal hemorrhage
Retina	Retinal dialysis (more common than retinal tears/holes) Retinal or subretinal hemorrhage Retinal edema (<i>commotio retinae</i> or <i>Berlin's edema</i> – <i>cherry red spot</i> seen) Macular hole
Optic nerve	Optic nerve avulsion Hemorrhage of optic nerve sheath <i>Traumatic optic neuropathy</i>

PENETRATING OCULAR TRAUMA

Types of Foreign Bodies

• *MC intraocular foreign body* – IOFB (90%) = *Iron and steel* (due to *chisel and hammer* type of injury).

Inert FB: Glass, plastics and porcelain; gold, silver, platinum and titanium.

FB that excites *suppuration*: zinc, nickel, mercury.

FB that causes *degenerative changes*: Iron, Copper.

Iritis

It is caused by *iron and steel*.

Earliest clinical feature is *anterior capsular cataract*, milky iron deposits on anterior capsule; iris is reddish brown stained – *heterochromia*; *plgментары retinopathy*; *diminished b-wave on ERG* – useful in monitoring retinal degeneration if extraction of IOFB is deferred; secondary glaucoma – all lead to decreased vision; pathologically iron is stained by the *Prussian blue* reaction.

Chalcosis

It is caused by *low copper content foreign body* and *brass*.

High copper content foreign body causes *violent endophthalmitis* and progression soon to *phthisis bulbi*.

Copper in eye causes *Kayser Fleischer ring* in *Descemet's membrane* of cornea; anterior *'sunflower cataract'*; *degenerative retinopathy* does NOT occur; *vision remains GOOD*.

Diagnosis of IOFB

• Radiography: for metallic foreign bodies (FBs) – *Caldwell Luc and lateral views*; *limbal ring method*.

• CT scan: good for metals.

• MRI is contraindicated in cases of metallic FBs.

• Use an ultrasound.

CHEMICAL INJURY TO EYE

• *Alkali injury* is more common (alkalis more widely used at home and in industry).

• *Alkali injury more dangerous* than acids (since they penetrate deeper); acids coagulate surface proteins resulting in a protective barrier.

• Common involved alkalis are *ammonia, sodium hydroxide and lime ('choona')*.

• Signs include *corneal epithelial defect* and *limbal ischemia* (limbus contains stem cells).

• *Thorough slit lamp examination* at presentation is NOT possible due to *severe pain and blepharospasm*.

Treatment

• *First treatment* is *copious irrigation with normal saline* for about 30 minutes.

• Particles of chemicals (like lime/*chuna*) *must be removed with forceps*.

• *Antibiotic ointment: tetracyclines* preferred (they are effective collagenase inhibitors, inhibit neutrophil activity and reduce ulceration).

• Cycloplegics

• *Ascorbic acid (vitamin C)*: improves wound healing and synthesis of collagen; topical sodium ascorbate may also be used.

• *Corticosteroid*: drops and ointment for the *first 7–10 days ONLY* – they reduce inflammation and symblepharon formation; *after 10 days they may cause corneal ulceration* and melting.

• Inhibition of collagenolysis and stromal damage: 10% *sodium citrate*; 5% *N-acetylcysteine* and 1% *medroxyprogesterone* eye drops may be used.

• In severely damaged eyes: *limbal stem cell transplantation* is used; *penetrating keratoplasty* and *keratoprosthesis* (K-PRO) may be necessary.

ORBITAL WALL FRACTURES

Walls of Orbit

Orbit Wall	Bones	Comments
Roof of orbit	Lesser wing of sphenoid Frontal	Defect in roof may cause <i>pulsatile proptosis</i> due to transmission of CSF pulsation from anterior cranial fossa to orbit
Lateral wall	Greater wing of sphenoid Zygomatic	Lateral anterior half of eye vulnerable to trauma since Lateral wall doesn't completely cover the eyeball
Floor (# floor = orbital blow out # - MC # of orbit)	Zygomatic Maxillary Palatine	<i>'Blow-out' fracture MC involves the floor</i> , esp. posteromedial portion of maxillary bone
Medial wall (<i>thinnest wall</i>)	Maxillary Lacrimal Ethmoidal Sphenoid	<i>Lamina papyracea</i> of medial wall is <i>paper thinnest</i> and perforated by foramina for nerves and blood vessels and hence <i>orbital cellulitis MC occurs through this secondary to ethmoidal sinusitis</i>

Orbital Wall Fractures

• Occurs due to high velocity object (> aperture of orbital margin i.e., 5 cm dia, such as tennis ball, shuttlecock or fist injury) striking the eye.

• *Pure blow-out fracture* does NOT involve orbital rim; impure fracture involves orbital rim and adjacent bones.

- **Blow-out fracture MC involves floor of orbit** along the thin bone covering the infraorbital canal.
- Signs
 - **Periocular ecchymosis**
 - **Infraorbital nerve anesthesia** (of lower lid, cheek, side of nose, gums)
 - **Diplopia** (mechanical entrapment of infr rectus or infr oblique muscle)
 - **Enophthalmos** (with severe fracture)
- CT scan: "**teardrop sign**" with orbital floor defect and contents in maxillary antrum.
- Treatment by surgical repair - especially within 2 weeks if muscle entrapment present.
- "**White eyes**" **orbital blow out fracture** (WEBOF) seen in < 18 years of age - NO visible external signs but muscle entrapment in floor causes recurrent activation of oculocardiac reflex leading to acute nausea, vomiting and headache - urgent surgical repair needed.
- **Pediatric patients** are at risk for "**trapdoor**" fractures as their bones tend to be cartilaginous and bendable.

EXTRA EDGE

- **Blow-in fractures:** here, bony fragments gets into the orbit reducing orbital volume; MC in **orbital roof in young children**.

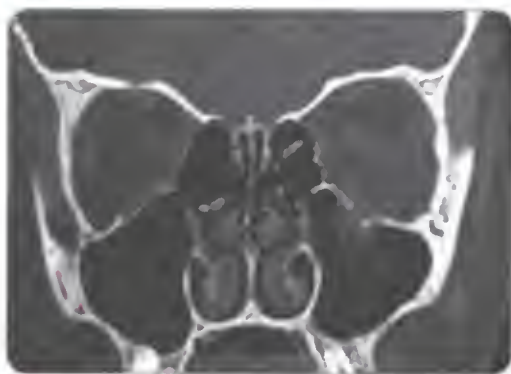


Fig. 17.75: Teardrop sign

EXTRAOCULAR MUSCLES

Muscle	Primary action	Subsidiary action	Nerve Supply	Insertions of recti from limbus
Medial rectus	Adduction		Oculomotor N (III)	Superior = 7.7 mm
Lateral rectus	Abduction		Abducent N (VI)	Lateral = 6.9 mm
Superior rectus	Elevation	Intorsion and Adduction	Oculomotor N (III)	Inferior = 6.6 mm
Inferior rectus	Depression	Extorsion and Adduction	Oculomotor N (III)	Medial = 5.5 mm (" SLIM ")
Superior oblique	Intorsion	Depression and Abduction	Trochlear N (IV)	
Inferior oblique	Extorsion	Elevation and Abduction	Oculomotor N (III)	

SOME DEFINITIONS

- **Visual axis:** (line of vision) passes from the fovea through the nodal point of fixation (object of regard).
- **Phoria** = latent squint; **Tropia** = manifest squint
- **Orthophoria** = perfect ocular alignment in the absence of any stimulus for fusion which is uncommon.
- **Heterophoria** = a tendency of the eyes to deviate when the fusion is blocked (latent squint).
- **Heterotropia** = a manifest deviation in which the visual axes do not intersect at the point of fixation.
 - Upward displacement of one eye relative to another is called **hypertropia** and a controlled upward imbalance a **hyperphoria**.
 - Downward displacement is termed a **hypotropia** and an imbalance is **hypophoria**.
- **Anatomical axis** is a line passing from the posterior pole through the centre of the cornea. Since the fovea is usually slightly temporal to the anatomical centre of the posterior pole of the eye, the visual axis does not usually correspond to the anatomical axis of the eye.
- **Angle Kappa:** is the angle subtended by the **visual and anatomical axes** and is about 5 degrees.
 - The angle is positive when the fovea is temporal to the centre of the posterior pole resulting in medial displacement of the corneal reflex.
 - A **large angle kappa** may give the appearance of a squint (pseudo squint) and is seen as a pseudo-exotropia following displacement of the macula following Retinopathy of prematurity when the angle may significantly exceed + 5 degrees.
- **Near point of convergence** is the **nearest point at which the eyes can maintain binocular fixation**. It is measured with the **RAF (Royal Air Force) rule**.
- **Near point of accommodation** is the **nearest point at which the eyes can maintain clear focus**. Also measured with RAF rule.

EXTRA EDGE

- III N. inferior division supplies MR, IR and IO; superior division supplies SR.

Easy method to remember extraocular muscle (EOM) actions

The actions of EOM is a straightforward question and should be answered correctly.

Basic concepts

- Primary action: is the action when the eye is in the primary position.
- Subsidiary action: are the additional effects on the position of the eye.

Read and remember the below statements

Horizontal recti have only one action (i.e. primary action only)

- Medial rectus: Adduction

- Lateral rectus: Abduction

AND

- All other muscles have one primary and two subsidiary actions.

AND

- Primary action of oblique muscles is torsion (intorsion or extorsion).

AND

- Primary action of superior rectus is elevation and inferior rectus is depression.

After going through the above statements

- JUST Remember the **mnemonic "SINRAD"** which means: All Superiors are INTortors; All Recti (obviously I am talking about only the 2 vertical recti) are ADductors.
- [The mnemonic also implies (inferiors are extortors and obliques are abductors) - but you don't need to remember this].
- With the above knowledge read the above table once; now take a paper and write down the actions once without looking. IT WORKS. And you won't forget even if you want to!

Mnemonic for EOM Nerve Supply

- **LR6(SO4)** = Lateral Rectus by VI cranial nerve (abducent); Superior Oblique by IV cranial nerve (trochlear) and the rest by III cranial nerve (Oculomotor).

ALSO KNOW

- **Superior oblique** - "**copying** (in exam) muscle"; ALSO called '**tramp's muscle**' - moves the eye 'down and out'. Superior oblique produces depression of the eye when the eye is adducted. Superior oblique paralysis causes NO obvious squint but **diplopia on looking down** - typically **while reading or climbing down stairs**.
- **Inferior oblique** - "**stargazer's muscle**" - produces elevation of the eye when the eye is adducted.
- **Pure elevation** of eyeball is by the superior rectus with opposite named (i.e. inferior) oblique
- **Pure depression** of eyeball is by the inferior rectus with opposite named (i.e. superior) oblique
- **TWISTED FACT:** When the eye is adducted 54 degrees, the superior oblique acts solely to depress the globe and when the eye is abducted 36 degrees, it solely intorts the globe - this means - **Superior Oblique depresses the globe in adduction and intorts the globe in abduction**; also similarly the **inferior oblique elevates the globe in adduction and extorts the globe in abduction**.

More Important Points about Extraocular Muscles

- **Inferior oblique** is the **ONLY** muscle that does NOT arise from the apex of the orbit.
- **Superior oblique** muscle is usually NOT paralyzed in retrobulbar block since the fourth cranial nerve is outside the muscle cone.
- **Levator Palpebrae Superioris (LPS)** is considered by some to be an extraocular muscle; It is supplied by a branch of **superior division of oculomotor nerve**; LPS acts as an **elevator of upper eyelid**.
- **Muller's muscle:** consist of **smooth muscle fibres**; supplied by **sympathetic nerve fibres**; sympathetic irritation leads to **retraction of lids** and paralysis leads to **Horner's syndrome**.
- **Orbicularis oculi** consist of orbital and palpebral parts - supplied by **facial nerve**.
- **Spiral of Tillaux** is an imaginary line joining the insertions of the four recti and is an important landmark when performing squint surgery.

OCULAR MOTILITY

- **Agonist-antagonist:** pairs are muscles of the same eye that move the eye in opposite directions. For example, the left lateral rectus is antagonist to the left medial rectus.
- **Synergists** are muscles of the same eye that move the eye in the same direction. For example the right superior rectus and the right inferior oblique act synergistically in elevation.
- **Yoke muscles** (contralateral synergists) are **pairs of muscles, one in each eye**, that produce **conjugate ocular movements**. For example the yoke muscle of the left superior oblique is the right inferior rectus; similarly yoke muscle of the right lateral rectus is the left medial rectus; similarly yoke muscle of right medial rectus is left lateral rectus.
- **Sherrington law of reciprocal innervation** (Inhibition) states that "increased innervation to an EOM (e.g. right medial rectus) is accompanied by reciprocal decreased innervation to its antagonist (e.g. right lateral rectus)"; **Mnemonic: "Sharing (Sherrington) should be reciprocal"**;
- **Hering's law of equal innervation** states that "during any conjugate eye movements, equal and simultaneous innervation is supplied to yoke muscles to move both eyes into the same direction of gaze". **Mnemonic - "Hearing (Hering's) should be equal (in both ears)"**.

Ocular Movements

- **Ductions** are monocular movements around the axes of Fick; they are abduction, adduction elevation, depression, extorsion and intorsion; tested by occluding one eye.
- **Versions** are binocular, simultaneous, conjugate movements (in the same direction); dextro and levo-versions; elevation and depression; dextroelevation and extrodepression; levoelevation and levodepression.
- **Vergences:** are binocular simultaneous, disjunctive/disjunctive movements: convergence and divergence.
- **Near triad:** accommodation, convergence and miosis for near vision.

Other Basic Considerations

- **Binocular single vision** grades on the **synoptophore: Simultaneous macular perception (I); Fusion (II) and Stereopsis (III)**.
- **Horopter:** is an imaginary plane in external space, all points on which stimulate corresponding retinal elements and are therefore seen singly and in the same plane.
- In **esotropia**, the diplopia is homonymous (**uncrossed** OR **harmonious**).

- In **exotropia**, the diplopia is heteronymous (**crossed**).
- **Microtropia** is a **small angle squint** (< 10 Prism diopters or 5 degrees) in which stereopsis is present but reduced and there is a relative amblyopia of the more ametropic eye. There is eccentric fixation and harmonious ARC.
- Sensory adaptations to strabismus (confusion and diplopia) in children is by **suppression** and **abnormal retinal correspondence (ARC)**.
- Motor adaptation to strabismus is by adopting an **abnormal head posture** (esp. in children); by face turn to right or left, head tilt to right or left and chin elevation or depression.

CLINICAL METHODS IN STRABISMUS

Stereopsis

- Stereopsis is the **perception of depth** — a three dimensional view of any object is obtained due to stereopsis.

Monocular (Nonstereoscopic) Clues to stereopsis

These are clues which give an idea about relative 3-D depth of objects:

- ▶ Motion parallax
- ▶ Linear perspective
- ▶ Overlay of contours
- ▶ Distribution of highlights and shadows
- ▶ Size of known objects
- ▶ Aerial perspective

Tests for Stereopsis

- TNO test
- Frisby test
- Titmus test (fly, circles or animals test)
- Frisby Davis distance stereo test

Methods for Measurement of Deviation

- **Prism bar test** — **most commonly used method in routine clinical practice** — either loose prisms or prism bars.
- **Hirschberg test** (corneal reflection test) — rough test — If reflex of a torchlight on cornea is midway between the pupil margin and corneal margin deviation is approx. 20 degrees and at corneal margin is approx. 45 degrees, and
- **Krimsky** and prism reflection tests.
- **Bruckner test:** used to detect **small angle strabismus** in infants; red reflex of a direct ophthalmoscope light shone into the eye is observed and both eyes compared the eye with strabismus will have faint glow.
- **Synoptophore**
- Maddox wing and Maddox rod are subjective measurement tests — of LIMITED value in the assessment of strabismus

Visual Acuity Testing in Children

Testing in Preverbal Children

- Fixation and following: using bright attention grabbing targets (a face is often best).
- Comparison: If one eye occlusion is strongly objected by the child, it indicated poorer visual acuity in the other eye.
- Rotational nystagmus test

Testing in Preverbal Children

- 10 prism diopter test
- Preferential looking tests (using **Teller**, Keeler or Cardiff acuity cards)
- Pattern VEP.
- At 2 years: Picture naming tests (Kay pictures)
- At 3 years: crowded letter tests
- Older children: ETDRS chart

Worth 4 Dot Test

- Procedure: Patient wears a **green lens in front of right eye** which filters all colors except green, and **red lens in front of left eye**, which, filters all colors except red. He then views a box with four lights: one red; two green and one white.
- Results:
 - ▶ If BSV (binocular single vision) is present all 4 lights are seen
 - ▶ If **all 4 lights are seen in the presence of manifest squint**, harmonious **ARC** (abnormal retinal correspondence) is present
 - ▶ If 2 red lights are seen, **right suppression** is present.
 - ▶ If 3 green lights are seen, **left suppression** is present.
 - ▶ If 2 red and 3 green lights are seen, **diplopia** is present.
 - ▶ If the **green and red lights alternate, alternating suppression** is present.

Tests for sensory anomalies

- ▶ Worth four dot test
- ▶ Bagolini striated glasses
- ▶ 4 prism diopter test
- ▶ Synoptophore (for grading binocular single vision and detecting abnormal retinal correspondence)

Diplopia

Diplopia (double vision) means that an object appears double. In diplopia, one image is distinct (true image) and the other is indistinct (false image).

- A. **Physiological Diplopia:** It is a normal phenomenon in which objects not within the area of fixation are seen double. It is easily demonstrated by looking at a near object with attention directed to a distant object.

- B. **Unocular Diplopia:** An object appears double when **only one eye remains open**. It occurs when two images of the same object fall on two different parts of the retina. More commonly, there is unocular polyopia due to multiple images.

Causes of Unocular Diplopia

- Immature cortical cataract (due to multiple water clefts within the lens).
- Subluxated clear lens (pupillary area is partly phakic and partly aphakic)
- Large peripheral iridectomy, iridodialysis or polycoria (multiple pupils)
- Retinal detachment due to dialysis when the retina becomes inverted.
- C. **Binocular Diplopia**—An object appears double when **both eyes remain open**. Binocular diplopia disappears when one eye is closed.

Causes of Binocular Diplopia

- Paralysis or paresis of the extraocular muscles (MC).
- Displacement of the eyeball by a space occupying lesion within the orbit.
- Mechanical restriction of movements of the globe (pterygium, symblepharon, thyroid ophthalmopathy).
- Acquired high anisometropia.

Crossed and Uncrossed

- ▶ Uncrossed diplopia: In **esotropia / convergent squint (LR palsy)**, the diplopia is **uncrossed (homonymous)**, that means the false image is on the same side of the deviation.
- ▶ Crossed diplopia: In **exotropia/divergent squint**, diplopia is **crossed (heteronymous)** that means the false image is thrown across the midline.

ESOTROPIA

Infantile Esotropia

- Idiopathic, develops **within first 6 months** of life.
- **Angle** is usually **fairly large** (> 30 prism diopters) and stable.
- Fixation is alternating in primary position and **cross fixating in side gaze**.
- **Nystagmus** is usually **horizontal**.
- Refractive error is usually normal for the age of the child.
- **Inferior oblique overaction** may be present initially or develop later.
- **Dissociated vertical deviation (DVD)** develops in 100% by age of 3 years.

- **Treatment:** Early surgical ocular alignment by age of 12 months (after correction of refractive errors and amblyopia).

Classification of Esotropia

Type	Criteria
Non-accommodative	Esotropia at distance = near fixation; NO change with refractive error
Accommodative	
Refractive (Normal AC/A ratio)	Esotropia at distance ³ near fixation; fully corrected by hyperopic correction for distance
Non refractive (High AC/A ratio)	Esotropia at near fixation > distance or manifesting only at near. Fully corrected by an additional hyperopic correction for near work.

SPECIAL SYNDROMES

- **Duane retraction syndrome:** *bilateral*; Eyes straight in primary position.; **Restricted abduction**; **Retraction of globe** and **narrowing of palpebral fissure** on adduction; **An upshoot or downshoot** in adduction; **Deficiency of convergence**;
- Huber's classification is used as below.
 - **Type I (MC): Limited abduction** with or without esotropia
 - **Type II: Limited adduction** with or without exotropia
 - **Type III: Limitation of both abduction and adduction** and any form of horizontal strabismus.
- **Brown's syndrome - superior oblique tendon sheath syndrome**; Defect of elevation in adducted position.
- **Mobius syndrome — Bilateral sixth nerve palsy**; horizontal gaze palsy present in 50% cases; Other systemic features: **B/L facial palsy - mask like face**; **Paresis of IX and XII cranial nerves (tongue atrophy)**; **mild mental handicap**; **limb anomalies**.
- **Double elevator palsy: III N nuclear lesion** causing **paralysis of superior rectus and inferior oblique muscle of the same eye**.

AMBLYOPIA

Classification of Amblyopia

Type	Examples
Stimulus deprivation	Unilateral/bilateral media opacity
Anisometropic	Hypermetropia of +1D spherical in one eye and + 7 D Sph in other eye

Contd...

Contd...

Type	Examples
Ametropic	Hypermetropia of +6 D Sph In both eyes
Meridional	- 6 D cylindrical × 180 degrees in one eye
Strabismic	Unilateral convergent squint

- **Amblyopia** is defined as a condition with unilateral or bilateral subnormal vision (at least 2 lines less than normal, or 2 lines less than fellow eye in unilateral cases) without any local fundoscopic abnormality, which is reversible if treated appropriately at the proper time.
- Vision in amblyopic eyes have certain characteristic features:
 - Single letter vision is better than when letters are presented in rows (as is the norm in visual acuity charts) - this is called **crowding phenomenon**.
 - Visual acuity **drops less when viewed through grey neutral density filters** compared to normal eyes.
 - **Decreased recognition, Vernier and grating acuity**
 - **Decreased contrast sensitivity and spatial localization.**
 - **Impaired pursuit eye movements and**
 - **Decreased saccadic amplitudes.**
- **Treatment:** Removal of opacity in the media; full correction of refractive errors; occlusion therapy.
- Other modes of therapy: **Atropine penalization** (to blur the sound eye); **pleoptics** (re-establishment of foveal fixation and may be helpful in older children); **CAM stimulator** therapy.

PARALYTIC SQUINT

Differences between Incomitant (Paralytic) Squint and Comitant Squint

- If **secondary deviation > primary deviation the squint is paralytic (incomitant)**. This is because increased innervation is required by the paretic muscle to move the eye into a certain position and this same amount of innervation goes to the normal muscle in the other eye, causing the secondary deviation to be greater than primary deviation.

Clinical Features	Incomitant Squint (Paralytic / Restrictive)	Comitant Squint
Magnitude of squint	Varies with eye position	Same in all positions
Diplopia	Usually present	Usually absent

Contd

DISEASES OF EYELIDS

Meanings of Certain Terms

- **Ankyloblepharon:** adhesion between upper and lower eyelid margins
- **Blepharoptosis:** dropping of upper eyelid
- **Distichiasis:** accessory row of eyelashes
- **Euryblepharon:** enlarged palpebral aperture
- **Madarosis:** loss of eyelashes
- **Trichiasis:** misdirected eyelashes
- **Tylosis:** hypertrophy of lid margins with consequent drooping
- **Entropion** is an inward turning of the eyelid with rubbing of the eyelashes on the conjunctiva and/or cornea.
- **Ectropion:** It is an outward turning of the eyelid away from the globe.



Fig. 17.76: Senile entropion—left lower lid



Fig. 17.77: Senile ectropion—left lower lid

Contd...

Clinical Features	Incomitant Squint (Paralytic / Restrictive)	Comitant Squint
ocular movements	Restricted	Full
late projection	Present	Absent
abnormal head posture	Usually present	Absent
secondary deviation	More than primary	Equal to primary

THE NEWBORN EYE

- Visual acuity at birth is about **6/240**.
- Visual acuity reaches **adult acuity by about 3 years**.
- Newborn is **hypermetropic by about + 2.5 D**
- In the new born, pupil is **miotic (constricted)**
- **Cornea** is large in newborns (10 mm) and **attains adult size by 2 years** (12 mm)
- **Retina** is fully developed at birth **except macula (which differentiates at 4-6 months)**.
- **Myelination** of optic nerve has reached the lamina cribrosa.
- **Orbit** is **more divergent** (50 deg) compared to adult (45°)

Stages of Binocular Vision

- **Fixation**
 - Monocular develops by 4-5 weeks in infants
 - Binocular develops by 3 months of age
- **Fusion-** corrective fusional reflex starts by first year and fully developed by 5-6 years
- **Binocular vision with stereopsis** fully developed by 7 years

EXTRA EDGE

- **Hess screen** and **Lees screen** are useful in **paralytic strabismus** (especially torsional deviations) to measure the degree of deviation and any progressive increase/decrease.
- **Forced duction test** and **Forced generation test:** To **differentiate restriction of eyeball movements** (ex: from trapped muscle in orbital fracture) **from extraocular muscle paralysis** (neurological defect).
- Drug causing **macular toxicity** when given **intravitreally - gentamicin**.
- **Birdshot retinochoroiditis** is a bilateral multifocal chorioretinitis; MC in females; A/w HLA -A29; flat creamy yellow spots resembling the pattern of birdshot scatter of a shotgun.
- **Toxic amblyopia:** Bilateral chronic retrobulbar neuritis caused by exogenous poisons: ethyl alcohol; methyl alcohol; ethambutol etc.
- Mild ptosis = 2 mm; moderate = 3 mm; severe = 4 mm.

Glands of Eyelids

Melbomian glands
(modified sebaceous glands)

Hordeolum internum is acute bacterial infection of **meibomian gland**. Treat with hot fomentation, NSAID's, Incision if required.

Chalazion is **Chronic lipogranulomatous** inflammation of Meibomian gland. Treat with **Incision and curettage (I and C)**; intralesional triamcinolone.

Meibomian (sebaceous) gland carcinoma may be misdiagnosed as **recurrent chalazion**

Glands of Zeis (sebaceous glands)
Glands of Moll (modified sweat glands)

Hordeolum externum is acute bacterial infection of glands of Zeis or Moll. Treat with NSAID's, hot fomentation. Incision if required.

Glands of Krause and Wolfring

Accessory lacrimal glands

Ptosis (Drooping Eyelid)

Myogenic

- **Myasthenia gravis**: Eye involved in 90% cases and is presenting feature in 60% case; **Cogan twitch sign**.
- **Myotonic dystrophy**: AD; gene on chromosome 19q
- **Ocular myopathy**: Chronic progressive external ophthalmoplegia
- **Simple congenital**: due to developmental dystrophy of levator muscle; unilateral or bilateral; **absence of upper lid crease**; associated with underlying superior rectus weakness; **compensatory chin elevation in severe bilateral cases**; astigmatism and anisometropia.
- **Blepharophimosis syndrome**

Neurogenic

- Third nerve palsy
- Horner syndrome
- **Marcus Gunn jaw winking syndrome**: there is retraction of ptotic eyelid with stimulation of ipsilateral pterygoid muscle (chewing etc).
- **III nerve misdirection**: bizarre movements of the upper lid with various ocular movements.

Aponeurotic

- **Involucional**: Age-related degenerative changes involving the levator aponeurosis.
- **Postoperative**: following manipulation or trauma to the superior levator complex by a **bridle suture**.

Mechanical

- Due to lid tumors

Congenital Ptosis

It is due to **developmental dystrophy of levator muscle**; unilateral or bilateral; **absence of upper lid crease**; **chin elevation** in severe bilateral cases; **lid lag on downgaze**; **astigmatism and anisometropia**.

Treatment of Ptosis

Fasanella Servat Operation

- **Indications**: Cases with levator function of **at least 10 mm** and provided **ptosis is no more than 2 mm**; includes most cases of **Horner's syndrome** and **very mild congenital ptosis**.

Levator Resection

- **Indications**: Any ptosis provided levator function is **at least 10 mm**; Everlusch's operation or Blaskowich's operation.

Frontalis Sling (Brow suspension) Indications:

- Severe ptosis with **poor levator function (4 mm or less)** - congenital ptosis.
- Marcus Gunn jaw winking syndrome.
- Aberrant regeneration of III nerve
- Blepharophimosis syndrome.
- Total III nerve palsy
- Unsatisfactory result from previous levator resection.



Fig. 17.78: Meibomian gland carcinoma can be mistaken for recurrent chalazion.

ORBIT

Orbital Fissures

Structures passing through the superior orbital fissure

- Oculomotor N (III N) two divisions
- Abducent nerve (VI N)
- Branches of ophthalmic division of trigeminal nerve (V N)
- Trochlear nerve (IV N)
- Lacrimal nerve, frontal nerve

- Recurrent lacrimal A.
- Superior ophthalmic V., inferior ophthalmic V.

SOF lies between greater and lesser wings of sphenoid; inflammation of SOF (Tolosa Hunt syndrome) may cause ophthalmoplegia and venous outflow obstructions

Structures passing through the inferior orbital fissure

- Maxillary division of trigeminal nerve
- Infraorbital artery
- Zygomatic nerve

- Branches of inferior ophthalmic vein draining into pterygoid venous plexus

IOF - Lies between greater wing of sphenoid and maxilla

Spaces of the Orbit

- **Subperiosteal Space**
- **Peripheral orbital space** (**peribulbar injection** is given here)
- **Central space** (within the muscle cone)
- **Tenon's space** (around the globe)

Proptosis

- **MC cause of unilateral or bilateral proptosis in adults - thyroid ophthalmopathy.**
- **MC cause of bilateral proptosis in children - metastatic neuroblastoma and/or leukemia.**
- **Intermittent proptosis** that is NON pulsatile and NOT a/w bruit is seen in **orbital varices**.
- **Pulsatile proptosis** with bruit and thrill is seen in
 - **carotico cavernous fistula.**
 - **Saccular aneurysms of ophthalmic artery**
 - **Deficient orbital roof** as seen with - meningocele or encephalocele, **NF-1**, traumatic disruption of orbital roof.
- **Proptosis in children** may be due to
 - Orbital cellulitis
 - Rhabdomyosarcoma
 - Optic glioma
 - Metastases. Neuroblastoma, Leukemia (chloroma, granulocytic sarcoma), Langerhans cell histiocytosis.

Surgeries

- **Enucleation**: Removal of **the entire globe (including sclera)**; contraindicated in **panophthalmitis**

- **Evisceration**: Removal of the contents of the globe **leaving the sclera and extraocular muscles intact**; the cornea is removed to provide access to the contents; suspected **malignancy is a contra-indication** for evisceration.

- **Exenteration**: Removal of the globe and the soft tissues of the orbit - **indicated in orbital malignancies; intraocular tumors invading the orbit; rhino-orbital mucormycosis.**

EXTRA EDGE

- After enucleation or evisceration a conformer (silicone or acrylic shell) is placed to support the conjunctival fornices; a temporary artificial eye can be placed at 6-8 weeks.

Calcification of the Globe

- **Retinal**
 - **Optic disc drusen**
 - **Retinoblastoma**, Retinocytoma
 - **Tuberous sclerosis** : "giant drusen", **astrocytic hamartomas**
 - **Epiretinal membranes**
 - **Retrolental fibroplasia** (retinopathy of prematurity)
 - **Coats disease**
- **Retinochoroidal**
 - **Chorioretinitis**: MC following Toxoplasmosis
- **Choroidal**
 - **Choroidal osteoma**: MC in patients with **tuberous sclerosis**
 - **Choroidal angioma**: occasionally calcify
- **Sclerochoroidal**
 - **Metastatic calcification**: hyperparathyroidism; pseudohypoparathyroidism, renal tubular acidosis
 - **Dystrophic calcification**: seen in elderly caucasians, mostly men
 - **Phthisis bulbi**: is the end result of major injury to the eye (trauma, infection) with a shrunken calcified 'lump' remaining
- **Scleral calcific plaques**

"Rings" in Ophthalmology

Ring	Seen in
Kayser-Fleischer's ring (K-F ring)	Wilson's disease (copper in the Descemet's membrane best seen on slit lamp)
Fleischer's ring	Iron deposition in epithellum at base of cone in keratoconus best seen with cobalt blue light on slit lamp
Weiss ring	Posterior vitreous detachment

Contd...

Contd...

Ring	Seen in
Wessley's ring	Immune ring in cornea viral/disciform keratitis
Vossius ring	A circular ring of pigment on the anterior lens surface due to impression of the contracted pupil on the lens , produced by trauma driving the cornea and iris backwards
Retinal 'Ring reflex'	Central serous retinopathy
Limbal ring	A metal ring sutured to the limbus and x-ray is taken to locate the position of intraocular metallic foreign body in relation to the ring
Capsule tension ring (CTR)	A.k.a endocapsular ring; To stabilize the capsular bag during IOL implantation into the capsular bag in case of zonular rupture/zonular dialysis

BLINDNESS

Definitions of Blindness

- The definition of Blindness under the National Programme for Control of Blindness (NPCB) has been modified in 2017 to be in line with WHO Definition (i.e. both are the SAME now): **"Presenting distance visually acuity less than 3/60 (20/400) in the better eye and limitation of field of vision to less than 10 degrees from center of fixation"**.
- The nomenclature of the scheme is also changed from 'National Programme for Control of Blindness' to 'National Programme for Control of Blindness and Visual Impairment'.

Types of Blindness

- Economic blindness:** Inability of a person to count fingers from a distance of 6 meters or 20 feet (Also called **"severe visual impairment"**: < 6/60 to 3/60)

- Social blindness:** Vision 3/60 or diminution of field of vision to 10°
- Manifest blindness (Legal blindness):** Vision 1/60 or just perception of light
- Absolute/Total blindness:** No perception of light
- Curable blindness:** That stage of blindness where the damage is reversible by prompt management (e.g. **cataract**)
- Preventable blindness:** The loss of blindness that could have been completely prevented by institution of effective preventive or prophylactic measures (e.g. **xerophthalmia, trachoma and glaucoma**)
- Avoidable blindness:** The sum total of preventable or curable blindness is often referred to as avoidable blindness.
- Also Know:** 6/6 to 6/18 - i.e., can see 6/18 or better is "normal" AND 6/24 to 6/60, i.e., cannot see 6/18 is "visual impairment"
- Note:** All above visual acuities are the best corrected visual acuity (BCVA) in the better eye (meaning BCVA with spectacles or lenses).
- References: NPCB website and Parson's 22nd edn, Pg 563.

Note

- Neuro-ophthalmology** including optic nerve disorders (optic neuritis, papilledema) and ocular muscle palsies (cranial nerve palsies) is discussed under **CNS chapter** (Pg 791)
- Ocular and orbital tumors** are covered under oncology chapter (Pg 958).
- NPCB** has been covered under **PSM chapter** (Pg 472).

CHAPTER

18

Otolaryngology

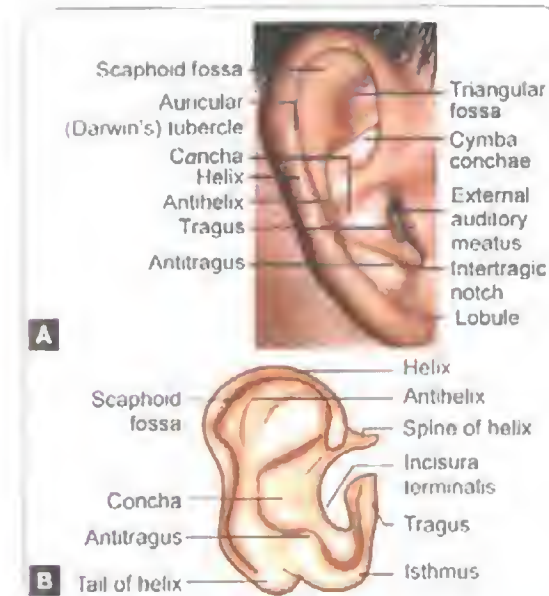
EAR

ANATOMY OF EXTERNAL EAR

It consists of (A) Pinna; (B) External auditory canal and (C) Tympanic membrane

Pinna/Auricle

- Pinna has single **yellow elastic cartilage** except at the **lobule** (where it is **absent**).
- Lateral surface has characteristic prominences and depressions; these are different in every individual (even among identical twins); hence **comparable to fingerprints** and **can allow for identification** of persons.
- Cartilage of pinna is continuous with the cartilage of external auditory canal; cartilage is covered with skin which is closely attached on lateral surface and **slightly loose on medial surface**.
- The cartilage itself is avascular and derives its supply of nutrients from the perichondrium covering it.

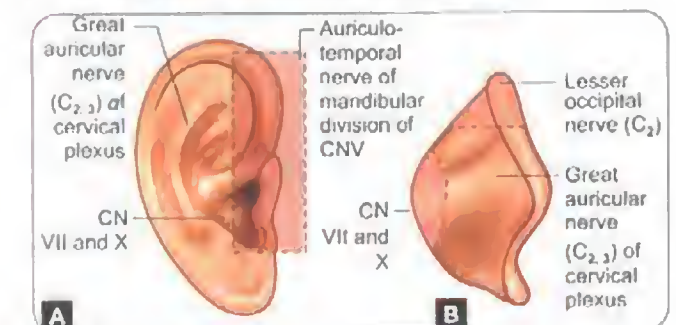


Figs 18.1A and B: External features of auricle. A. Photographic; B. Diagrammatic representation

More about pinna

- 'Boxer's ear':** Stripping of the perichondrium from the cartilage as occurs following injuries that cause **hematoma** can lead to cartilage necrosis and so called 'boxer's ear'.
- Incisura terminalis:** Area between the crus of the helix and tragus; It is devoid of cartilage; **Clinical importance:** An incision made in this area does NOT cut through the cartilage and is used for **Endaural approach** in surgery.
- A thin layer of skin closely adherent to the perichondrium covers pinna. So infection of the skin can readily pass into the cartilage to cause **perichondritis**.

- Pinna has **3 extrinsic muscles** 1. Auricularis anterior, 2. Auricularis superior and 3. Auricularis posterior; all attached to epicranial aponeurosis and **supplied by the facial nerve**.
- Intrinsic muscles** are 6 in number and are small and inconsistent.
- Arterial supply of Pinna:** **Posterior Auricular** (main artery), superior auricular branch of external carotid artery.
- Lymphatic drainage:** From posterior surface → lymph nodes at mastoid tip. From tragus and upper part of anterior surface → preauricular nodes; rest of auricle → upper deep cervical nodes.
- Nerve supply:** Shown in following figure.



Figs 18.2A and B: Nerve supply of right pinna: A. Lateral surface; B. Medial surface

External Auditory Canal (EAC)

- Develops from **dorsal part of the first branchial cleft/groove**.
- Length in adult = 24 mm (same as length of adult eye)**; S-shaped curve.

Cartilaginous part—outer 1/3 (8 mm)

- Deficient posterosuperiorly; has hair follicles, **sebaceous/ceruminous glands** (modified apocrine glands); since hair follicles present here **'furuncles'** forms more commonly here.
- Mixture of cerumen, sebum and desquamated cells is ear wax.
- Has two fissures/deficiencies in the anterior part called as **Fissures of sanctorini** through which parotid or superficial mastoid infection can appear in the canal and vice versa.

Bony part—inner 2/3 (16 mm)

- This part has **NO** hair follicles or glands.
- 5 mm lateral to tympanic membrane**, bony meatus is narrow and called **isthmus** (Foreign body lodgement site).
- Foramen of Huschke** is a deficiency present in anteroinferior part of bony canal in children upto 4 years of age, permitting infection to and from the parotid.
- Blood supply: External carotid artery.**
- Nerve supply:**
 - Anterior wall and roof: **Auriculotemporal nerve**
 - Floor and posterior wall: **Auricular branch of vagus (Arnold nerve)**—this nerve mediates the following two interesting phenomena:
 - Vasovagal reflex**—While cleaning the EAC, patient may develop **coughing**, bradycardia, syncope and even cardiac arrest.
 - Appetite**—Because of vagal innervation, instilling spirit.
 - Posterior wall also receives innervation from **facial nerve (hitzelberger's sign—hypoesthesia of the posterior meatal wall is seen in case of facial nerve injury)**.

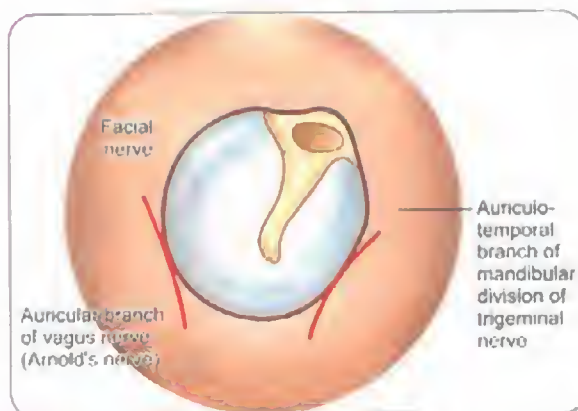


Fig. 18.3: Nerve supply of external auditory canal

Tympanic Membrane

- Almost **horizontal at birth**; in adult it forms an **angle of 55 degrees** with the floor of the external canal.
- 10 mm height; 9 mm width and 0.1 mm thick.
- Total surface area = **85 sq mm** (effective vibrating area 55 sq mm).
- It is **pearl grey** in color; lateral surface is concave.
- Layers** of tympanic membrane: Outer—Epithelial (from ectoderm); Middle—Fibrous (from mesoderm); Inner—Mucosal (from endoderm); When a tympanic membrane perforation heals spontaneously; it heals in two layers as it is often closed by squamous epithelium before fibrous elements develop.
- Gasserian fissure** has the **anterior malleolar ligament**.

Parts of tympanic membrane

► Pars tensa is the vibrating surface:

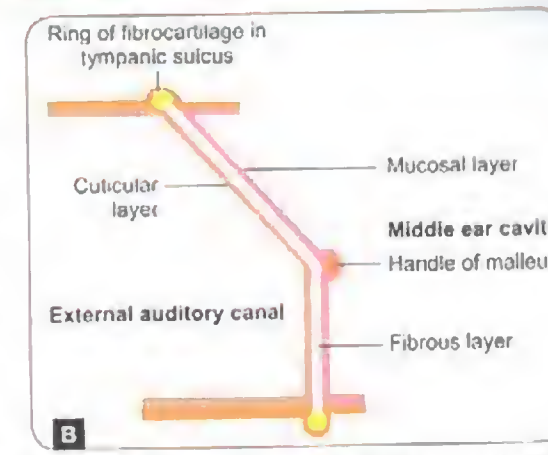
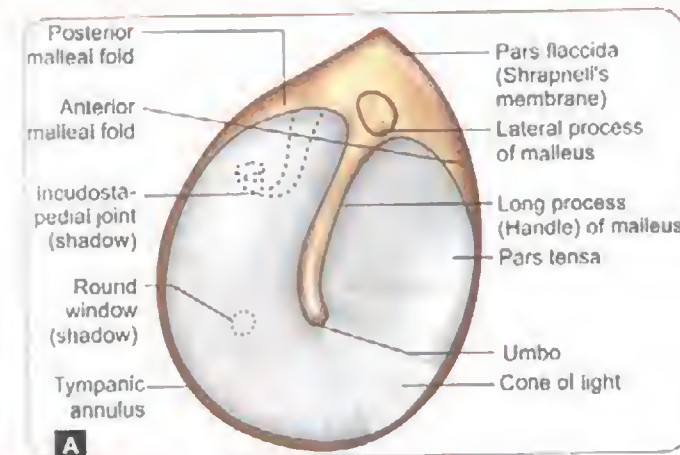
- Periphery is thickened to form a fibrocartilaginous ring called the **annulus tympanicus**
- This ring is deficient above in the form of a notch called the **notch of rivinus**
- The central part is tented inwards at the level of tip of handle of malleus and is called as **umbo** (point of maximum inward convexity of TM), **most reliable landmark** in otoscopy
- Cone of Light** is seen in **Antero inferior quadrant**. (Cone of **LA**ight).

► Pars flaccida (Shrapnell's membrane) is flaccid to allow movement of head of malleus; it is situated above the lateral process of malleus and between the notch of rivinus and anterior and posterior malleolar folds; it is crossed internally by chorda tympani nerve.

- Blood supply of tympanic membrane:** Vessels are present only in connective tissue layer of the lamina propria:
 - Deep auricular branch and anterior tympanic branch of **maxillary artery**
 - Twigs from **stylomastoid branch of posterior auricular artery**
 - Several twigs from **middle meningeal artery**.

Nerve Supply of Tympanic Membrane

Outer surface	Inner surface
<ul style="list-style-type: none"> Anteroinferior part by auriculotemporal nerve Posterosuperior part by auricular branch of vagus nerve 	<ul style="list-style-type: none"> Tympanic branch of Glossopharyngeal nerve—(Jacobson's nerve) (through tympanic plexus)



Figs. 18.4A and B: A. Tympanic membrane showing attic, malleus handle, umbo, cone of light and structures of middle ear seen through it on otoscopy; B. Three layers of tympanic membrane

Tympanic membrane MCQ facts

- Central perforation** in pars tensa—safe CSOM
- Marginal or attic perforation in pars flaccida—unsafe CSOM
- Multiple perforations: Tuberculosis**
- Multiple blebs/hemorrhagic blebs: Bullous myringitis** (mycoplasma, influenza virus)
- Granulation tissue** on TM: Granular myringitis
- Hemorrhagic blebs, petechiae: Barotruama**
- Central perforation: Tubotympanic (safe) CSOM**
- Marginal or attic perforation: Atticoantral (unsafe) CSOM**
- MYringotomy incision** is made in the **PosteroInferior quadrant ('MY PIE')**.

ANATOMY OF MIDDLE EAR CLEFT

Middle ear cleft in the temporal bone consist of (A) tympanic cavity (middle ear), (B) Eustachian tube, and (C) mastoid air cell system.

Anatomic Divisions of Tympanic Cavity (Middle Ear)

Mesotympanum

- Lies opposite the pars tensa
- Narrowest part of middle ear**; transverse dia = 2 mm (**MN**)
- Contents: Handle of malleus, long process and lenticular process of incus, stapes, oval window, round window, tensor tympani and chorda tympani nerve
- Inferior incudal space, anterior and posterior **pouch of von Troeltsch** lies in mesotympanum.

Epitympanum/attic

- Lies above pars tensa and medial to lateral attic wall and Shrapnell's membrane
- Widest part of tympanic cavity (transverse dia = 6 mm)
- PRussuk space** lies in **EPitympanum** ('PG entrance **PREP**')
- Contents: Head and neck of malleus, body and short process of incus

Hypotympanum

- Lies below the level of pars tensa
- Transverse dia = 4 mm
- It contains the **protympanum**—the portium of middle ear around the eustachian tube opening.

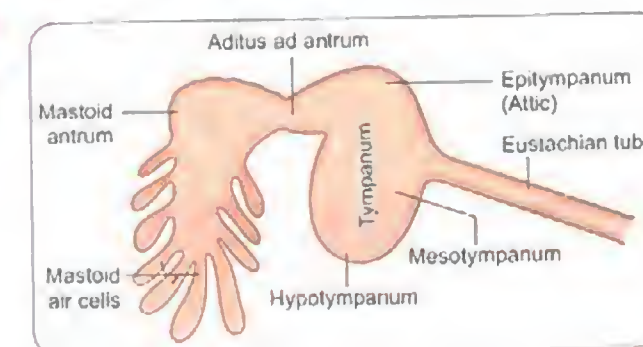


Fig. 18.5: Parts of middle ear cleft

EXTRA EDGE

- Anterior tympanic recess** or **supratubal recess** refers to a small compartment within epitympanum seen on CT imaging.

Middle Ear (Tympanic Cavity)

- It is **biconcave space** with 6 walls/sides.
 - **Roof** is formed by **thin tegmen tympani**; roof separates tympanic cavity from the **middle cranial fossa**; **tegmen tympani** is formed both by petrous and squamous part of temporal bone and the **petro squamous line which does not close until adult life**—can provide a route of access for infection into the **extradural space** in children.
 - **Floor** (jugular wall) is by a thin plate of bone (**Pars tementalis**) separating the tympanic cavity from the jugular bulb; at the junction of floor and medial wall is a small opening which allows entry of **tympanic branch of glossopharyngeal nerve** into the medial ear.
 - **Lateral wall** is formed by **tympanic membrane** and to some extent by **bony outer attic wall** called the **scutum of Lady**.
 - **Anterior wall** (carotid wall): It has 3 important structures from above downwards: (a) Canal for tensor tympani muscle, (b) **Eustachian tube orifice**, (c) Wall of carotid canal.

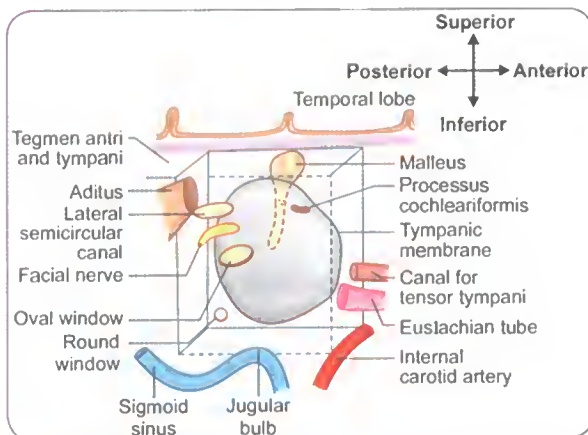


Fig. 18.6: Six boundaries of tympanum. Medial wall is seen through the tympanic membrane

Medial wall

- Separates **tympanic cavity** from inner ear
- It has **Pramantary** (Basal turn of cochlea); Fenestra ovalis (**Qval window**) closed by footplate of stapes; Fenestra Rotunda (**Raund window**) closed by **secondary tympanic membrane**; **Fallapian canal** with the facial. **N.** in it; ampullary prominence of the **harizontal** (Lateral) semicircular canal. ('**PORN harizontal**').
- Anterior to oval window lies a book-like projection called the **pracessus cochlearifarmis** for tendon of **tensar tympani**. The cochleariform process marks the level of the genu of the facial nerve, which is an **important landmark for surgery of the facial nerve**.

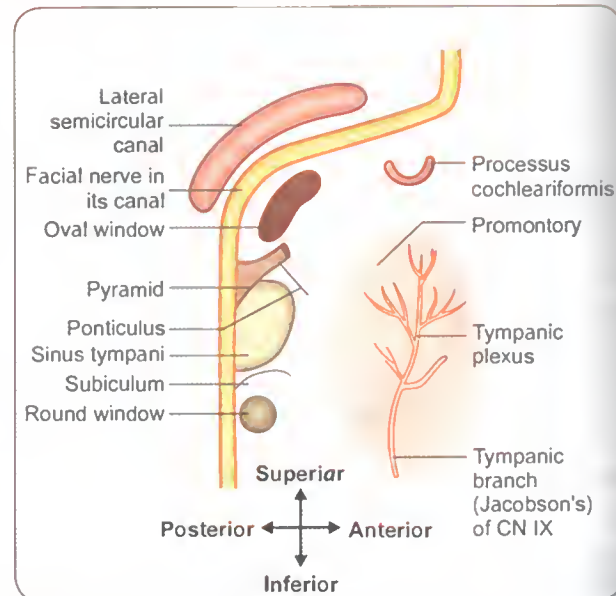


Fig. 18.7: Medial wall of middle ear

Posterior Wall

- It has an opening above (**aditus ad antra**) which leads to mastoid antrum.
- A bony projection called the **pyramid** that contains stapedius muscle.
- Fossa incudis** lies in epitympanic recess and contains short process of incus.
- An opening for exit of chorda tympani nerve.
- Facial nerve runs in the posterior wall just behind the pyramid.

Contents of Tympanic Cavity

- Auditory Ossicles**
 - **Malleus and Incus** are derived from the **1st arch**; **Stapes** develops from **Second arch** except its footplate and annular ligament which are derived from the otic capsule.
 - **MALLEus**: It is shaped like a **MALLet** (hammer), most lateral bone; 7.5–9 mm long; parts are head, neck, anterior process, lateral process and handle.
 - **INCus**: It is shaped like an **anvIl**; the **largest** of the three ossicles; placed **in between** malleus and stapes; parts are body, short process, long process and lenticular process (Note: **Lenticular process** is sometimes k/a, the **fourth ossicle** as it is a **sesamoid bone**).
 - **STapes**: Shaped like a **STirrup**; it is the **ShorTest bone of the body**; placed most medially; stapes consists of a head, neck two crura and foot plate; **footplate**

of stapes is held on the oval window by **annular ligament**; footplate is about 3 mm long and 1.4 mm wide.

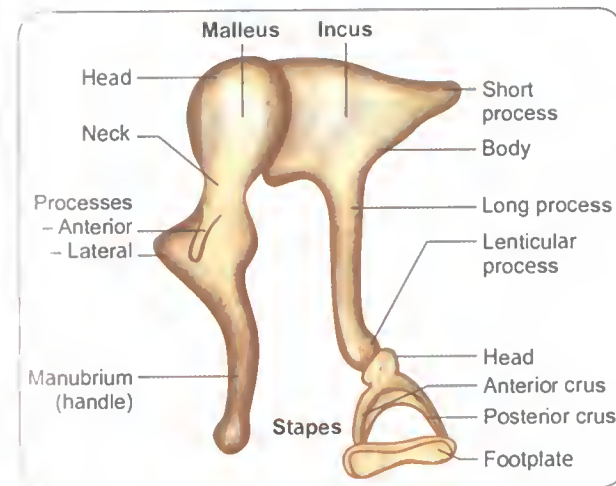


Fig. 18.8: Middle ear ossicles

- Joints of the ossicles:**
 - The **Incudo-Malleolar joint—SADdle joint (I M SAD!)**; Incudostapedial joint—**Ball and socket joint**; Note: Both are **synovial joints** and **diarthrodial joint**.
 - Stapedial: Labyrinth joint is a **syndesmotomic joint**.
 - Ossicles conduct sound energy from the tympanic membrane to oval window and then to inner ear fluid.
- Muscles viz.**
 - **Tensor tympani** develops from **1st Arch**: Contraction pulls handle of malleus medially, testing tympanic membrane to reduce the force of vibration in response to loud noise; supplied by: **Mandibular nerve (V₃)**.
 - **Stapedius** develops from **2nd Arch**: Contraction, usually in response to loud noise, pulls the stapes posteriorly and prevents excessive oscillation; supplied by **nerve to stapedius branch of facial nerve**.
- Tympanic plexus**

Nerve supply of middle ear	Blood supply of middle ear	Lymphatic drainage of middle ear
Tympanic branch of Glossopharyngeal nerve (nerve of Jacobson); tympanic branch of sympathetic	Arteries supplying the walls and contents of the tympanic cavity arise from both the internal and external carotid system:	Middle ear → retropharyngeal and parotid nodes Eustachian

Nerve supply of middle ear	Blood supply of middle ear	Lymphatic drainage of middle ear
plexus around internal carotid artery	<ul style="list-style-type: none"> ▪ Inferior tympanic artery (branch of ascending pharyngeal artery) ▪ Anterior tympanic artery ▪ Stylomastoid artery 	tube → retropharyngeal group

Mastoid Antrum

- It is an air sinus in the **petrous temporal bone**
- Mastoid **develops from squamous and petrous bone**
- Types of mastoid antrum: Pneumatized (80%); Sclerotic (20%); Mixed (Diploeic)**
- The mastoid antrum but not the air cells are well developed at birth. Pneumatization begins in the first year and is **complete by 4–6 years of age**
- Boundaries of mastoid antrum are:
 - Roof, formed by the tegmen antri
 - **Lateral wall**, by squamous part of temporal bone
 - Medial wall, by the petrous bone
 - Posterior wall and floor, by the mastoid bone
 - Anteriorly, it communicates with attic through aditus ad antrum.

More MCQs points

- **MacEwen's triangle (Suprameatal triangle)**: Formed by **suprameatal crest** above; **posterosuperior margin of the bony external canal** below; behind by an arbitrary line extending tangentially upward from the posterior meatal wall. **Suprameatal Spine of Henle** is situated in this triangle. It is the **landmark of mastoid antrum** during mastoidectomy operation. The antrum lies 15 mm deep to the surface. Clinically it is **palpated in the cymba cancha** of the pinna.
- **Korner's septum** is **persistence of petrosquamous suture** in the form of a bony plate; Korner's septum is surgically important as it **may cause difficulty in locating the antrum and the deeper cells**, and thus lead to **incomplete removal of disease at mastoidectomy**. Mastoid antrum cannot be reached unless the Korner's septum has been removed.

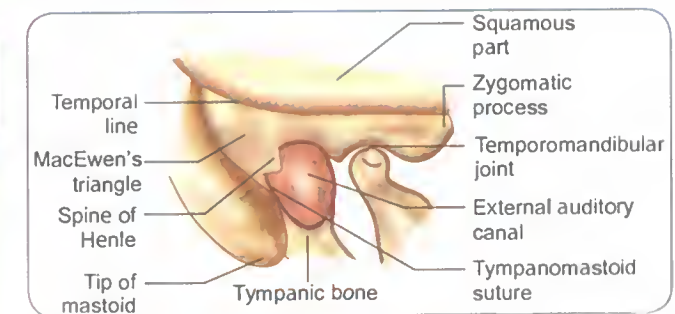


Fig. 18.9: MacEwen's triangle. Surface landmark for mastoid antrum

Eustachian Tube (Pharyngotympanic Tube)

- Connects tympanic cavity with the nasopharynx; helps to equalize pressure on both sides of tympanic membrane
- Eustachian tube = **36 mm** (reached by the age of **7 years**); lateral 1/3 (i.e. 12 mm) is bony; medial 2/3 (i.e. 24 mm) is fibrocartilaginous.
- In adults it is placed at an angle of 45° with sagittal plane while in infants it is short, wide and placed horizontally.
- Muscles of Eustachian tube:**
 - **Tensor palati** (dilator tube is a part of it) supplied by branch of mandibular nerve—medial fibers (dilator tuba) opens the tube when it contracts
 - **Levator palati** supplied by pharyngeal plexus through Xth cranial nerve; **Salpingopharyngeus**.
- Arterial supply** = branches from ascending pharyngeal artery, middle meningeal artery and artery of pterygoid canal (both branches of maxillary artery).
- Venous drainages = to pterygoid venous plexus.
- Nerve supply = by tympanic plexus.
 - Lymphoid tissue of Eustachian tube is called tubal tonsil—**Gerlach tonsil**.
 - **Ostmann's pad of fat** keeps the tube closed and prevents reflux of nasopharyngeal secretions into the middle ear.

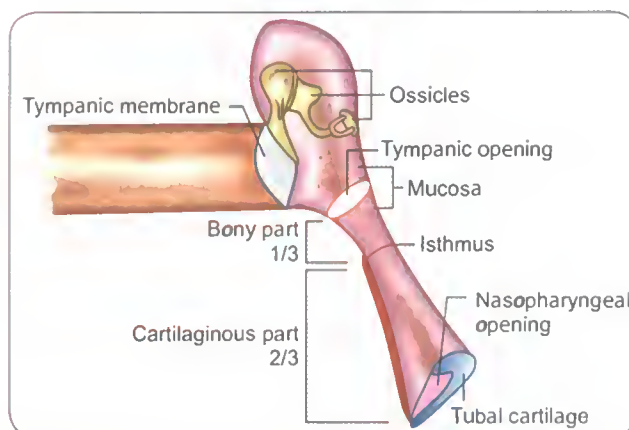


Fig. 18.10: Eustachian tube anatomy (horizontal section)

ANATOMY OF THE INNER EAR

- It consists of a **bony labyrinth** contained within the petrous temporal bone along with the **membranous labyrinth**.
- It serves the most important function of **hearing and equilibrium**.

Bony Labyrinth

- Bony labyrinth** consists of a series of tubes in the temporal bone filled with **perilymph** (rich in Na⁺, similar to ECF); includes **bony cochlea**, **vestibule** and **semicircular canals**.

Bony cochlea

- Is **32 mm long** and shaped like a spiral canal, which winds **two and half times** around the central bony axis called **modiolus**.
- Arising from the modiolus is a thin shelf of bone which spirals upwards within the lumen of the cochlea as the bony **Spiral lamina**—it gives attachment to the **basilar membrane**.
- Spiral lamina divides the cochlear canal into **upper scala vestibuli** and **lower scala tympani**. The scala vestibuli and scala tympani are continuous with each other through **helicotrema** at the apex of cochlea.
- Scala vestibuli** is closed by the footplate of stapes, which separates it from the air filled middle ear.
- Scala tympani** is closed by secondary tympanic membrane; it is also connected with the subarachnoid space through the **cochlear aqueduct** (infections like meningitis can gain access to inner ear through this cochlear aqueduct).

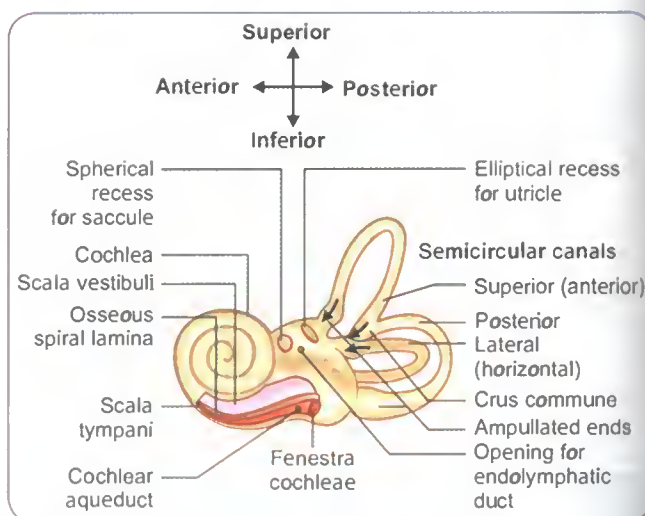


Fig. 18.11: Medial wall of left bony labyrinth seen from lateral side after the removal of its lateral wall

Semicircular Canals

- Are **3 in number**—Superior (anterior); Posterior and Lateral (horizontal)—lie at right angles to each other.

- Ampulla:** One end of each canal dilates to form the AMPULLA which contains the vestibular sensory epithelium and opens independently in vestibule.
- Crus commune:** Formed by the non-ampullated ends of the superior and posterior semicircular canal. So the 3 semicircular canals open in vestibule by '5' openings.
- '**Solid angle**' is the area of bony labyrinth that lies between the semicircular canals.

Vestibule

- Central portion of the bony labyrinth.
- Posteriorsuperior wall: Has '5' openings of the semicircular canals.
- In the lateral wall lies the **oval window**.

Medial Wall

- Spherical recess:** For the macula of saccule; Carries fibers of inferior vestibular nerve
- Elliptical recess:** For the macula of utricle
- Cochlear recess:** For the cochlear nerve
- Vestibular recess:** Carries the endolymphatic duct.

Membranous Labyrinth

- Membranous labyrinth:** A second series of tubes within the bony labyrinth filled with **endolymph** (rich in K⁺, similar to ICF); includes cochlear duct (within the cochlea), utricle and saccule (within the vestibule) and semicircular ducts.

Cochlear duct (membranous cochlea)

- Also called **scala media**. It is a blind coiled tube.
- It appears triangular on cross-section and has three walls formed by
 - The basilar membrane, which supports the **organ of corti**
 - The Reissner's membrane which separates it from the **scala vestibuli**
 - The stria vascularis, which contains vascular epithelium and is concerned with secretion of **endolymph**
- Cochlear duct is connected to the saccule by **ductus reuniens**
- The length of basilar membrane increases as we proceed from the basal coil to the apical coil. So higher frequencies of sound are heard at the basal coil while lower ones are heard at the apical coil.
- Hair cells** (located within the organ of Corti) are the sensory elements in both vestibular apparatus (spatial orientation) and cochlea (hearing).

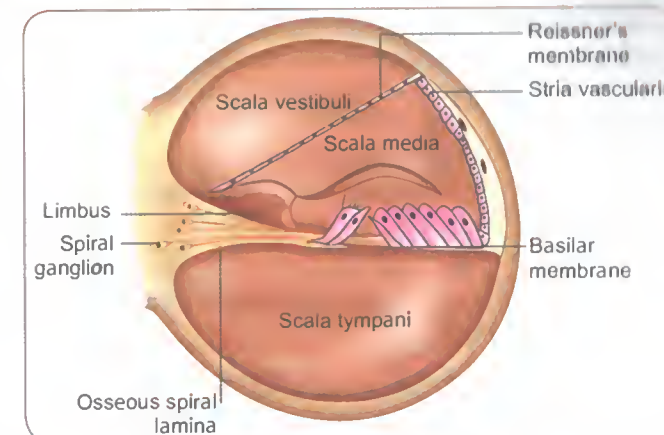


Fig. 18.12: Structure of cochlear canal after its cut section

Blood Supply of the Inner Ear

- Arterial supply:** It is from the **labyrinthine artery** which arises usually from the **anterior inferior cerebellar artery** and occasionally from basilar artery.
- Venous drainage:** It is through **three veins** namely **internal auditory vein of cochlear aqueduct** and **vein of vestibular aqueduct** which ultimately drain into **inferior petrosal sinus** and **lateral venous sinus**.

EXTRA EDGE

- Blood supply to the inner ear is **independent** of blood supply to middle ear and bony otic capsule, and there is no cross circulation between the two.
- Blood supply to cochlea and vestibular labyrinth is **segmental**, therefore, independent ischemic damage can occur to these organs causing either cochlear or vestibular symptoms.
- Nerve supply of inner ear:** by superior and inferior vestibular nerves.

Inner Ear Fluids (Perilymph and Endolymph)

- Perilymph **resembles extracellular fluid and is rich in Na ions**. It fills the space between the bony and the membranous labyrinth. It communicates with CSF through the **aqueduct of cochlea** which opens into the scala tympani near the round window.
- Endolymph fills the **entire membranous labyrinth** and **resembles intracellular fluid, being rich in K ions**. It is **secreted by the secretory cells of the stria vascularis of the cochlea** and by the **dark cells** (present in the utricle and near the ampullated ends of semicircular ducts).

Endolymphatic Duct and Sac

- Endolymphatic duct** is formed by the union of two ducts, one each from the saccule and the utricle. It passes

through the vestibular aqueducts. Its terminal part is dilated to form **endolymphatic sac** which lies under the dura on the posterior surface of the petrous bone.

- **Donaldson's line** is the surgical landmark for endolymphatic sac (which is situated **inferior** to this line). It passes through horizontal SCC bisecting the posterior SCC.

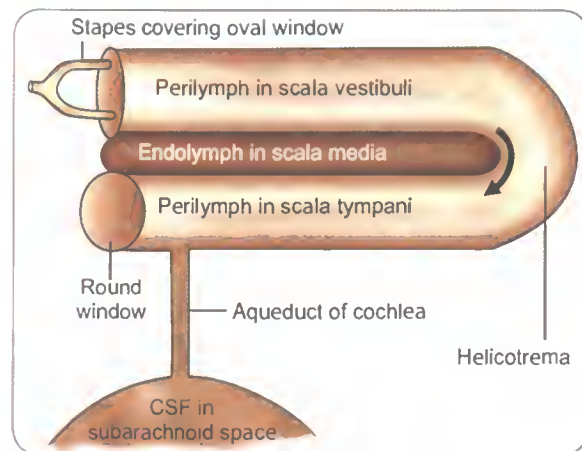


Fig. 18.13: Cochlea: Peri- and endolymphatic systems relations with cerebrospinal fluid (CSF)

Extra Points

- The **ponticulum** is the ridge of bone between the oval window niche and sinus tympani.
- The **subiculum** is a ridge of bone between the round window niche and sinus tympani.
- Only one-third of the population has a pneumatized petrous portion of the temporal bone.
- **Scala communis** is where the scala tympani joins the scala vestibuli. The **helicotrema** is at the apex of the cochlea where the two join.
- **Porus acusticus** is the 'mouth' of the internal auditory canal. The canal is divided horizontally by the crista falciformis.
- **Trautmann's triangle** is demarcated by the bony labyrinth, the sigmoid sinus, and the superior petrosal sinus or dura. Infection into the posterior cranial fossa can spread through this triangle and can be approached by removing the bone in between the triangle.
- **Scutum** is the thin plate of bone which constitutes the lateral wall of the epitympanum. It is part of the squamosa.

Structures of ear fully formed at birth

- Middle ear
- Ossicles: Malleus, Incus and Stapes
- Labyrinth
- Cochlea

- Mastoid tip does not develop till 2 years; hence postaural incision to open the mastoid before this age needs to be modified to avoid injury to the facial nerve.
- **Eddy currents** in the external auditory meatus do not allow water to reach TM while swimming.
- **Glasserian fissure** in the middle ear transmits anterior tympanic branch of maxillary artery, anterior ligament of malleus and chorda tympani nerve through canal of Huguier
- Organ of corti is filled with cortilymph.
- In the very young infants, **Hyrtl's fissure** affords a route of direct extension of infection from the middle ear to the subarachnoid spaces. The fissure closes as the infant grows. Hyrtl's fissure extends from the subarachnoid space near the glossopharyngeal ganglion to the hypotympanum just inferior and anterior to the round window.
- **Meckel's cave** is the concavity on the superior portion of the temporal bone in which the **gasserian ganglion (cranial nerve V)** is located.
- **Dorello's canal** is between the petrous tip and the sphenoid bone. It is the groove of the **VI cranial nerve (abducens)**.
- **Vertical crest** of the **internal auditory canal** is called **Bill's bar**.

Referred Otalgia

- Otalgia (ear pain) due to referred pain from head and neck regions which are innervated by nerves that also supply to the ear.
- Common causes of referred otalgia:

Via V CN
(Trigeminal nerve, auriculotemporal branch)

- **Dental** disease: Caries tooth, apical abscess, impacted molar, malocclusion
- **TM joint** disease: Bruxism, osteoarthritis, dislocation, ill-fitting denture, Costen's syndrome
- **Oral cavity**: Any ulcers of tongue or oral cavity
- **Sphenopalatine** (Sluder's) and trigeminal neuralgia

Via IX CN
(glossopharyngeal)

- **Oropharynx**: acute tonsillitis; peritonsillar abscess, tonsillectomy; ulcers of soft palate, tonsil and its pillars
- **Base of tongue**: Malignancy or TB
- Elongated **styloid process**

Via X CN (vagus)

- Malignancy or ulcerative lesions of vallecula, epiglottis, larynx or laryngopharynx, esophagus

Via C2 and C3
(spinal nerves)

- **Cervical** spondylosis, injuries of cervical spine, TB spine (caries spine)

Via CN VII
(facial nerve)

- Geniculate neuralgia, Bell's palsy and herpes zoster oticus

EXTRA EDGE

- **Costen syndrome**—TM joint dysfunction due to dental mal-occlusion causing masseter spasm and referred ear pain.

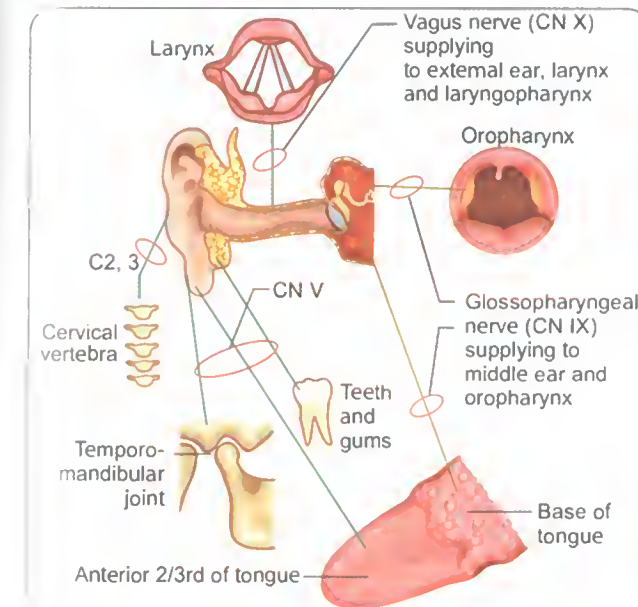
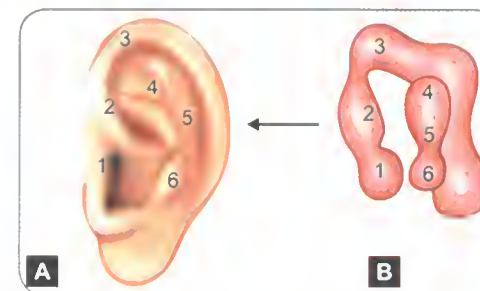


Fig. 18.14: Referred otalgia. Common causes of referred otalgia and nerve supply of ear

DEVELOPMENT OF EAR

Pinna

- Develops from the six tubercles (Hillocks of His).
- Attains adult configuration by 20th week.
- Contributing arches: Only tragus develops from 1st arch, rest of pinna develops from 2nd.



Figs. 18.15A and B: Development of pinna. A. From six Hillocks of His; B. Around the first branchial cleft (1 from first and 2-6 from second branchial arch)

Applied Anatomy

- **Preauricular sinus**:
➤ These are **blind tracks** lined by **squamous epithelium** and are a result of **incomplete fusion of the tubercles** between first and second arch.

- It represent a **remnant of the first branchial cleft**.
- If it gets infected, **excision of the sinus tract** is necessary.
- **Opening** is found in front of the ascending limb of the helix.
- **Sinogram** with radiopaque dye is done to know the extent of the tract.

- **Anotia** = absence of the pinna; **Microtia** = small deformed pinna
- Surgical reconstruction of pinna is done at 6 years of age using costal cartilage (because pinna attains adult size by 5 years of age).

External Auditory Canal (EAC)

- Develops from: **Dorsal end of the 1st Branchial cleft**.
- **Applied anatomy**: Cartilaginous part of the EAC has '2' fissures (**fissures of santorini**).
- **Importance**: Infection from the mastoid and parotid can pass into each other. Bony part of the EAC antero-inferior part has a deficiency known as **foramen of Huschke** (persists till the age of four).

More MCQ points

- **Tubotympanic recess** (which develops from the dorsal part of the first pharyngeal pouch, and also receives a contribution from the second pouch): Its **proximal part gives rise to pharyngotympanic tube** and to **epithelial lining of the middle ear**
- **First pharyngeal arch** (mandibular arch) derivatives: **Malleus and incus** are derived from the dorsal and of **Meckel's cartilage**; tensor tympani is derived from the mesoderm
- **Second pharyngeal arch** derivatives: Stapes, Stapedius
- The ossicles of the ear **fully ossify in the fourth month of intrauterine life**. They are the first bones in the body to do so.
- **Mastoid process**: Develops after the first year of life; continues to grow upto 19 years after birth
- **Stapedius** supplied by facial nerve; **tensor tympani** by mandibular nerve.

Inner Ear

- **Membranous labyrinth**: Derived from a specialized area of **surface ectoderm** overlying the developing hindbrain.
- **Bony labyrinth**: It is formed from the **mesenchyme** surrounding the membranous labyrinth.
- The **cochlea develops by 20th week** of gestation and the fetus can hear in the uterus of the mother (remember Abhimanyu's story from Mahabharata!).

PHYSIOLOGY OF AUDITORY SYSTEM

Organ of Corti

- It is the sense organ of hearing and is situated on the basilar membrane in scala media. Important components of the organ of corti are:

- **Tunnel of corti**, which is formed by the inner and outer rods. It contains a fluid called cortilymph.
- **Hair cells**: They are important receptor cells of hearing and transduce sound energy into electrical energy.

	Inner hair cells	Outer hair cells
Total number	3,500	12,000
Rows	One row	3-4 rows
Shape	Flask shaped	Cylindrical
Nerve supply	Primarily afferent fibers	Mainly efferent fibers
Development	Develop earlier	Develop later
Function	Transmit auditory stimuli	Modulate function of inner hair cells
Vulnerability	More resistant	Easily damaged by ototoxic drugs and high intensity noise
Generation of Otoacoustic emissions	No	Yes (Outer hair cells)

- **Supporting cells**: *Deiters cells*; *Pillar cells*; *Hensen's cells*, *Boettcher's cells*.

- **Note**: With aging, hair cells at the base are lost more than at the apex; hence hearing loss is more for higher frequencies than lower.

- **Tectorial membrane**: It consists of gelatinous matrix with delicate fibers. It overlies the organ of corti. The shearing force between the hair cells and tectorial membrane provides the stimulus to hair cells.

EXTRA EDGE

- Type I cells correspond to the inner hair cells of organ of Corti and Type II cells correspond to the outer hair cells.

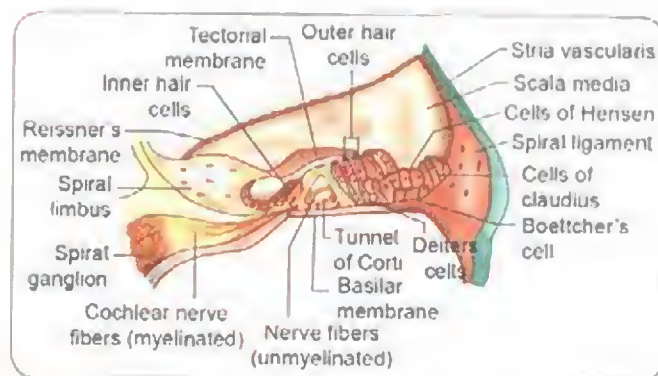
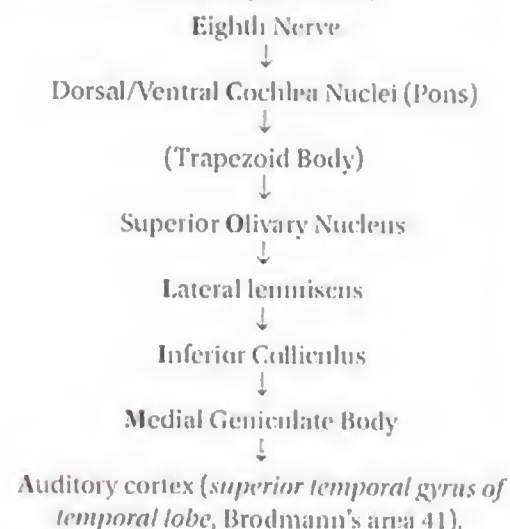


Fig. 18.16: Structure of organ of Corti

AUDITORY PATHWAY (PATHWAY OF HEARING)

The peripheral processes of the bipolar neurons of spiral ganglion (first order neurons) innervate the inner hair cells of organ of corti. The central processes of bipolar neurons pass through the tractus spiralis foraminosus at the medial end of internal acoustic meatus, where they assemble to form the cochlear nerve (Eighth nerve).



Mnemonic = 'ECOLIMA'

- The auditory fibers travel via the ipsilateral and contralateral routes and have multiple decussation points. Thus each ear is represented in both cerebral hemispheres.

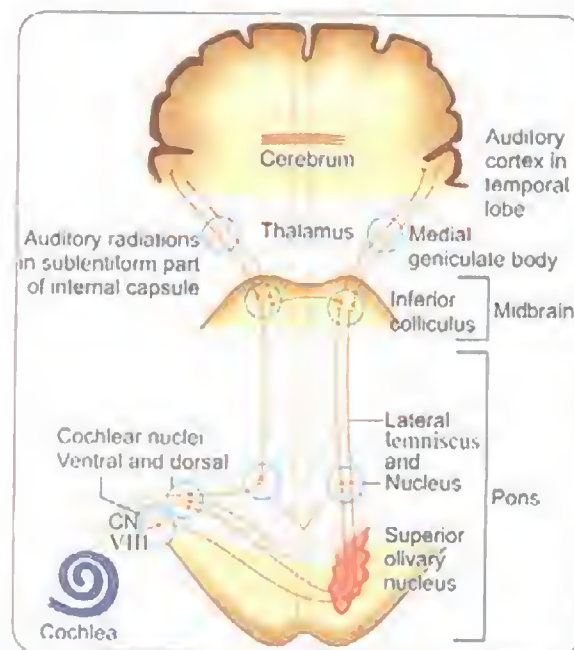


Fig. 18.17: Central auditory pathways

MECHANISM OF HEARING

The mechanism of hearing can be broadly divided into:

- **Mechanical conduction** of sound (external and middle ear conductive apparatus)
- **Transduction** of mechanical energy to electrical impulses (sensory system of cochlea)
- **Conduction of electrical impulses to the brain** (CN VIII, brainstem, thalamus and temporal lobe neural pathways).

1. Conduction of Sound

Pinna

Pinna increases sound pressure by 6 dB (2 times). It helps in:

- **Collection**: Gather sound arriving from an arc of 135 degrees.
- **Localization**: Determine the origin of sound.
- **Concentration**: Horn shaped concha acts like a megaphone and concentrates the sound at the entrance of EAC.

External Auditory Canal

- Along with pinna it can increase sound pressure at tympanic membrane by 15-22 dB at 4000 Hz.

Impedance Matching Mechanism (Transformer Action) of Middle Ear

Middle ear converts sound of greater amplitude, but lesser force, to that of lesser amplitude and greater force - this is impedance matching/transformer action.

1. **Hydraulic action of tympanic membrane (TM) (Hydraulic lever)**: The area of TM is much larger than the stapes footplate. Therefore TM provides large hydraulic ratio between the TM and stapes footplate.

- **Areal ratio** = functional area of TM/area of stapes footplate = $45 \text{ sq mm} / 3.2 \text{ sq mm} = 14:1$.

2. **Curved membrane effect (Catenary lever)**: Movements of the TM are more at the periphery than the center; this provides **2 times** gain in sound pressure at malleus.

3. **Lever action of the ossicles (Ossicular lever)**: Ossicular chain conducts sound from TM to the oval window. Lever action of the ossicles (handle of the malleus is 1.3 times longer than the long process of the incus) provides a **mechanical advantage—lever ratio of 1.3**. (Ossicular leverage ratio).

- The product of areal ratio (hydraulic action of TM) and lever action of ossicles = **Total transformer ratio** is 18:1 (14×1.3). It offers a 25 dB increase in sound energy arriving at the cochlea.

- BUT according to Wever and Lawrence; 55 sq mm is taken as effective vibratory area of TM. So areal ratio becomes 17:1 and transformer ratio becomes 22:1. So in a question if asked - first choice for answer would be 18:1 and second choice would be 22:1.

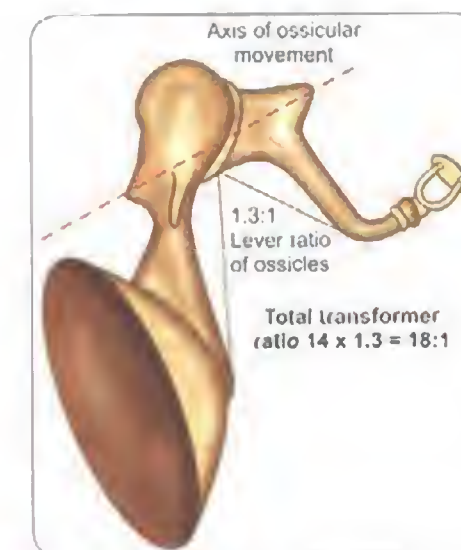


Fig. 18.18: Transformer function (ratio 18:1) of middle ear. Hydraulic effect of tympanic membrane (14:1) and lever action of ossicles (1.3:1)

Phase differential between Oval and Round Window

- This acoustic separation helps in movement of the perilymph contributing to hearing. Phase differential between the oval and round window contributes 4 dB when the TM is intact.

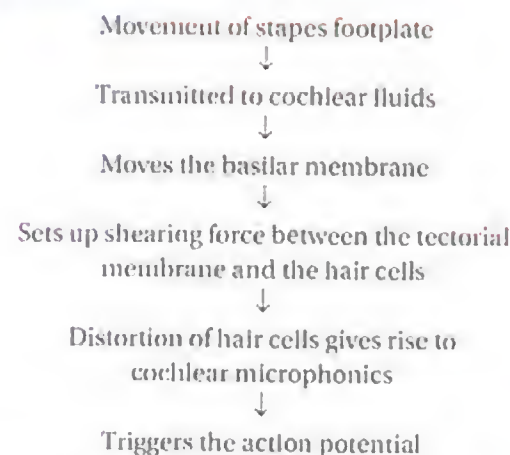
Natural Resonance of External and Middle Ear

- Inherent anatomic and physiologic properties of the external and middle ear allow certain frequencies of sound to pass more easily to inner ear due to their natural resonances.
- As seen in the following table, the greatest sensitivity of sound transmission is between 500 and 3000 Hz and these are the frequencies most important in day-to-day conversation.

Natural resonance and efficiency of auditory receptors

External auditory canal	3000 Hz
Tympanic membrane	800-1600 Hz
Middle ear	800 Hz
Ossicular chain	500-2000 Hz

2. Transduction



- A sound wave depending on its frequency reaches maximum amplitude at a particular place on the basilar membrane and stimulates that segment (*traveling wave theory of von Bekesy*).
- Higher frequencies** are represented in the **basal turn** and the progressively **lower tones towards the apex** of the cochlea—means high frequency waves travel a short distance and die whereas low frequency waves travel a long distance.
- Hair cells located at the **base** of the basilar membrane are most excited by **high-pitched** tones, whereas hair cells at the **top (apex)** of the basilar membrane are excited by **low pitched** tones.

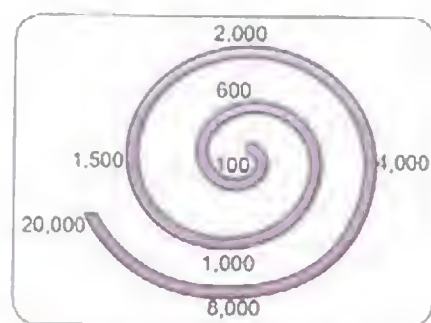


Fig. 18.19: Tonotopic gradient in cochlea. Higher frequencies are represented in the basal turn and the progressively lower tones toward the apex of the cochlea

ELECTRICAL POTENTIALS OF COCHLEA AND VIII NERVE

- | | |
|-----------------------------|---------------------|
| • Endocochlear potential | |
| • Cochlear microphonic | • From cochlea |
| • Summating potential | |
| • Compound action potential | • From nerve fibers |

- Endocochlear potential:** The resting potential of **+80 mV** direct current (DC) is recorded from scala media; it is generated from the stria vascularis by Na^+/K^+ ATPase pump and provides source of energy for cochlear transduction.
- Cochlear microphonic**, is an alternating current (AC) potential, generated by the **outer hair cells of the organ of corti**.
- Summating potential (SP)**, is a DC potential which is generated by the **inner hair cells** in response to sound.
- Compound (auditory nerve) action potential (AP)** representing the composite all or none firing of the auditory nerve fibers.

NEURAL PROCESSING OF AUDITORY INFORMATION

Pitch determination (encoding of frequency)	Cochlea
Determination of loudness (encoding of intensity)	Cochlear nerve
Feature detection	Higher auditory centers
Localization of sound	Higher auditory centers (relay nuclei in the brainstem, i.e. superior olivary nucleus)

PHYSIOLOGY OF VESTIBULAR SYSTEM

Vestibular System Peripheral Receptors

Cristae

They are located in the ampullated ends of the three semicircular canals. These receptors respond to **angular acceleration and deceleration**. It has 2 types of hair cells: type 1 and type 2.

Maculae

- Maculae:** They are located in otolith organs (i.e. utricle and saccule). **Utricle**—Senses **HOrizontal** linear acceleration (**'UTHQ'** in Hindi); **Saccule**—Senses **vertical** linear acceleration; Utricle + saccule—Both sense gravity and position of head in space
- A macula consists mainly of two parts:
 - A **sensory neuroepithelium**, made up of type I and type II cells, similar to those in the crista.
 - An **otolithic membrane**, which is made up of a gelatinous mass and on the top, the crystals of **calcium carbonate** called **otoliths** or **otoconia**.

VESTIBULAR NERVE

- Vestibular or **Scarpa's ganglion** is situated in the lateral part of internal acoustic meatus. It contains bipolar cells.

- The distal processes of bipolar cells innervate the sensory epithelium of the labyrinth while its central processes aggregate to form the vestibular nerve.
- A unique feature of vestibular neurons is their high frequency of discharge with an average of 90/second.
- The **inferior vestibular nerve** supplies the maculae in the saccule. A branch of the inferior vestibular nerve called as **singular nerve** supplies the hair cells of cristae in the **posterior SCC**.
- The **superior vestibular nerve** supplies cristae of superior and lateral SCC and macula of utricle.

CENTRAL VESTIBULAR CONNECTIONS

There are 4 vestibular nuclei—superior, medial, lateral and descending (inferior). Their afferents and efferent connections are given in the following table.

Afferent and Efferent Connections of Vestibular Nuclei	
Afferents connections	Efferents connections
Peripheral vestibular receptors (semicircular canals, utricle and saccule)	Nuclei of CN III, IV, and VI via medial longitudinal bundle
Cerebellum	Cerebellum (vestibulocerebellar fibers)
Spinal cord	Vestibulospinal tract
Vestibular nuclei of the opposite side	Vestibular nuclei of the opposite side
Reticular formation	Autonomic nervous system
	Cerebral cortex (temporal lobe) through thalamus

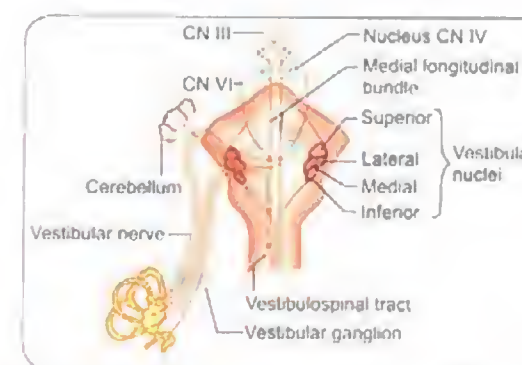


Fig. 18.20: Vestibular pathways

PERIPHERAL VESTIBULAR APPARATUS

Utricle and Saccule

- The utricle and saccule lie in the posterior part of bony vestibule.
- It receives the five openings of the three semicircular ducts.

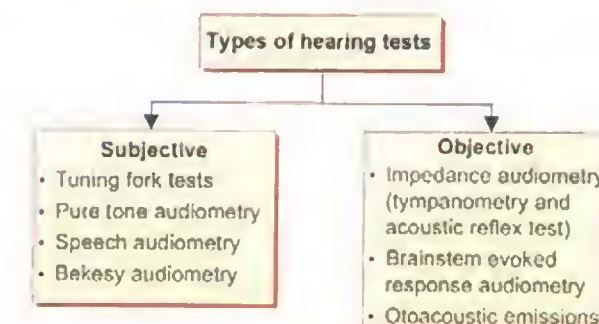
- It is connected to the saccule through utriculosaccular ducts.
- The sensory epithelium of the **utricle and saccule** is called the **macula** and is concerned with **linear acceleration and deceleration**.
- In the utricle, **tip links** in the hair cells are involved in **regulation of distortion activated ion channels**.

Semicircular Canals

- They are three in number and correspond exactly to the three bony canals. They open in the utricle.
- The ampullated end of each duct contains a thickened ridge of neuroepithelium called **crista ampullaris**—detects **angular acceleration**.
- Ewald's law:** When a semicircular canal is stimulated, it tends to elicit nystagmus in its own plane.
- Coriolis effect:** When the subject's head is tilted about an axis which is perpendicular to the main axis of rotation, spatial disorientation will be experienced. It is a specific type of angular acceleration (i.e. sensed by semicircular ducts) that **causes motion sickness in space craft** due to rotation of earth.

ASSESSMENT OF HEARING

Types of Hearing Tests



TUNING FORK TESTS

Test	Rinne's test	Weber's test
Normal	Air conduction > bone conduction, i.e. AC > BC, i.e. Positive Rinne	NO lateralization, i.e. It is central
Conductive deafness	AC < BC, i.e. Negative Rinne	Sound is lateralized to the poorer or deaf ear
Sensorineural deafness	AC > BC but of low volume and shorter duration—called low positive Rinne	Sound is lateralized to the better ear

Contd...

Test	Rinne's test	Weber's test
Severe unilateral sensorineural deafness	BC is apparently heard longer in the deaf ear. This is a False Negative Rinne as BC is actually being heard by the opposite ear (Normal ear), while AC is not heard	Usually Weber is lateralized to the diseased side in negative Rinne, but if it is lateralized to the healthy side it signifies False Negative Rinne as a result of severe sensorineural deafness

- **Most useful tuning fork** for hearing tests is **512 Hz** as the intensity of sound lasts longer for patients understanding the response and the sound is different from ambient noise.
- Weber's test is quite sensitive as difference of only **3–5 dB** hearing level can result in lateralization.

Gelle's Test

- In a person with normal hearing, compression of the air in the external canal by Siegle's speculum reduces hearing by bone conduction.
- When **Stapes is fixed in Otosclerosis**, BC is unaffected.

Absolute Bone Conduction Test

- Bone conduction is a measure of cochlear function; In ABC test patient's BC is compared with that of the examiner; EAC of BOTH patient and examiner should be occluded.
- In **conductive deafness ABC is normal**.
- In **sensorineural deafness ABC is shortened**.

Schwabach Test

- Similar to ABC test BUT the EAC is NOT occluded.
- Schwabach is reduced in sensorineural deafness and lengthened in conductive deafness.

Bing Test

- This test is similar to Rinne's and is based on the improvement in bone conduction perception in the normal subject *when the external auditory meatus is occluded*.

Tests for nonorganic hearing loss (malingering)

- **Stenger's test**
- **Chimani Moose test** (Weber's lateralization test)
- **Lombard's test**

Tests for nonorganic hearing loss (malingering)

- Loud voice test (Erhard's test)
- Cochleo Palpebral test
- Stethoscope test
- Two speaking tubes test
- Audiometric test
- Doerfler Stewart test
- Hypnosis

AUDIOMETRIC TESTS

Pure Tone Audiometry

- **MC type of audiometry.** Air conduction and bone conduction are tested by pure tone through an audiometer at **octave steps**, i.e. 125, 250, 500, 1000, 2000, 4000, and 8000 Hz. Intensity of sound is increased or decreased for each of above frequencies from 0 dB to 100 dB. The **threshold of hearing** at each frequency in AC and BC is plotted on a graph called **audiogram**.
- The frequency range **between 500 and 3000 Hz** is **important in clinical practice**.

Method

- Audiometry done in a **soundproof** room.
- **First Air Conduction (AC)** and then Bone Conduction (BC) is recorded separately for each ear.
- The pure tones are presented to the ears by headphones (for AC) and vibrator (for BC).
- The graph on which these thresholds are charted is called **audiogram**.
- For **Right ear** **Red** color and for left ear blue color pencils are used.
- For AC, continuous line and for **BC**, interrupted (**Broken**) line is used.

Uses of Pure Tone Audiometry

- Audiometric results are **quantified results** showing the **degree of deafness** (mild—profound), **type of deafness** (conductive/sensorineural) and **hearing threshold**.
- Used for diagnosis of conductive deafness with **Alt Bone (A-B) gap**.
- **High frequency** audiometry used in monitoring **ototoxicity**.
- The type and necessary settings for **hearing aid** can be determined.
- Speech Reception Threshold (**SRT**) can be predicted.

- **Otosclerosis—Cahart's notch** at 2000 Hz in BC
- **Acoustic trauma—Sudden dip** at **4000 Hz** in both BC and AC tracing
- **Rollover curve**—Retrocochlear lesion
- **Rising type curve**—Ménière's disease

Speech Audiometry

- **Speech reception threshold:** The SRT is the softest intensity **spondee words** (two syllable words with equal stress on each syllable such as oatmeal, shipwreck, daydream, etc.) that an individual can repeat at least 50% of the time.
- **Word recognition: (speech discrimination score)** is the ability to repeat correctly a phonetically balanced words (monosyllabic words—bus, day, red, etc.) at suprathreshold intensity.

Other Audiometry Terminologies

- **Pure-tone average (PTA)** is the average of hearing sensitivity at 500, 1000, and 2000. This average should approximate the speech reception threshold (SRT), within 5 dB, and the speech detection threshold (SDT), within 6–8 dB.
- **Speech detection threshold (SDT):** Also termed the speech awareness threshold (SAT), is the lowest intensity speech stimulus that an individual can detect at least 50% of the time.
- **Bekesy Audiometry**
 - A **self-recording** type of audiometry; **rarely performed** these days
 - Interpretations of various types of tracings are:

Type I	Conductive hearing loss
Type II	Cochlear hearing loss
Type III and IV	Retrocochlear lesions
Type V	Nonorganic hearing loss
- **Impedance audiometry**
 - This measures the **impedance** (resistance) which is offered by the **conducting mechanism of tympanic membrane and middle ear** and their compliance (suppleness) to sound pressure transmission.
 - There are two basic tests performed—**tympanometry** and **acoustic reflex** testing.

Tympanometry

- Sound delivered is **220 Hz**
- A microphone picks up reflected sound
- Air pump increases and decreases air pressure in the external auditory canal
- A tympanogram is the graphic representation of change in impedance or compliance as the pressure in the ear canal is changed.

Types of tympanogram

- **A:** Normal (normal middle ear pressure)
- **As:** Reduced compliance at ambient pressure (**otosclerosis**)
- **Ad:** Increased compliance at ambient pressure (**ossicular discontinuity**)
- **B:** **Flat or dome shaped** tympanogram (fluid in middle ear – **otitis media**) or tympanic membrane perforation, cerumen occlusion.
- **C:** **Rounded tympanogram;** maximum compliance at pressures more than 100 mm of H₂O (**negative pressure** in middle ear—**eustachian tube dysfunction**).

Acoustic Reflex/Stapedial Reflex/Tympanic Reflex

- During tympanometry, an intense tone elicits contraction of the stapedius muscle = **acoustic/stapedial reflex**. Tone can be presented in one ear and reflex picked up from same or contralateral ear!
- **Principle:** Intense/loud sound striking the ear → interaural muscles (stapedius contract) → Stapes footplate rocks in the oval window and stiffens the ossicular chain and tympanic membrane → ↑ in the impedance of the middle ear system.
- **Sound intensity** used for acoustic reflex testing = **70 to 100 dB** (loud sound).
- **Reaction time** for tympanic reflex is **40–160 milliseconds**.

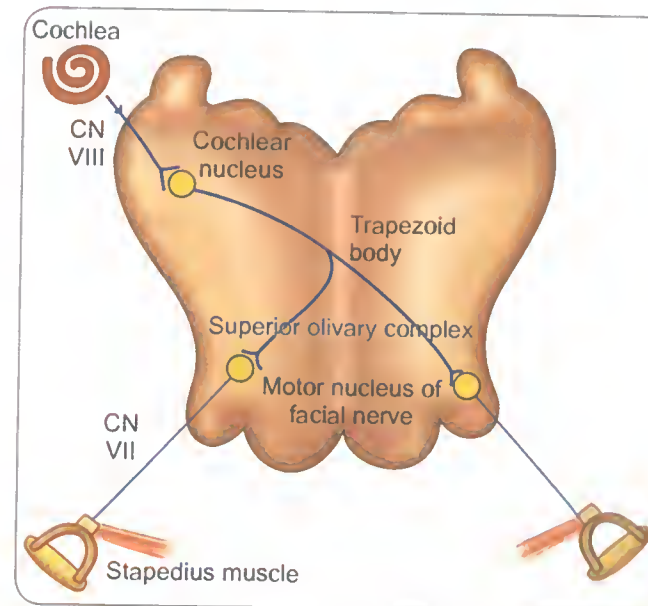


Fig. 18.21: Cut-section of the pons showing acoustic reflex pathways

Causes of Absent Stapedial Reflex

Afferent pathway	Efferent pathway
Middle ear diseases <ul style="list-style-type: none"> Otosclerosis Ossicular discontinuity Atelectasis 	VII nerve diseases <ul style="list-style-type: none"> Facial palsy Ramsay hunt syndrome
Cochlear/VIII nerve/superior olivary complex lesion <ul style="list-style-type: none"> Severe SNHL Acoustic neuroma Multiple sclerosis 	Stapedius muscle involvement <ul style="list-style-type: none"> Post stapedectomy Myasthenia gravis

Use of Stapedial Reflex Test

- For identifying the level of lesion in VII nerve (facial nerve) palsy—**anatomic localization**.
- Assessment of **acoustic reflex decay** helps **differentiate sensory (cochlear) from neural/retrocochlear (eighth nerve disease) hearing losses**. In neural hearing loss, the reflex adapts or decays with time.
- In malingeringers; To test hearing in infants and young children; elimination of middle ear pathology.

OTOACOUSTIC EMISSION (OAE)

- Otoacoustic emissions (OAEs) are low intensity sounds (acoustic signals) emitted from the cochlea to middle ear and into the external ear canal where they are recorded with microphones inserted into the external auditory canal.
- OAE are generated by acute mechanical contraction of the **Outer hair cells**; **Absence of OAE = structurally damaged or nonfunctional outer hair cells**; OAE do NOT disappear in eighth nerve pathology as cochlear hair cells are normal.

Types of OAE

- **Spontaneous OAE**
 - Present in healthy normal hearing persons where hearing loss is not more than 30 dB
 - May be absent in 50% of normal persons; limited clinical use
- **Evoked OAE**, i.e. elicited by a sound stimulus:
 - Transient evoked otoacoustic emissions (TEOAE's)
 - Distortion product OAE's (DPOAE's)

Uses

- OAE's used as a **screening test of hearing in neonates**; mentally challenged patients after sedation.
- OAE's help to distinguish cochlear from retrocochlear hearing loss as they are absent in cochlear but present in retrocochlear lesions.

ELECTROCOCHLEOGRAPHY

- This measures the earliest **evoked potentials** generated in the cochlea and the auditory nerve in response to auditory stimuli within **first 5 milliseconds**.
- Receptor potentials recorded include cochlear microphonics, summing potentials and action potential of the VIII nerve.
- Electrocochleography (EcoG) is useful (i) to find threshold of hearing in infants and children to within 5–10 dB (ii) to differentiate lesions of cochlea from those of VIII nerve.
- Test is **useful** in the diagnosis of **Ménière's disease where a SP:AP is elevated**.

BRAINSTEM EVOKED RESPONSE AUDIOMETRY (BERA)

- Aka Auditory Brainstem Response (ABR) or Auditory Nerve and Brainstem Evoked Potentials (ABEP).
- Earliest recorded at **27–28 weeks** gestational age; Best test to detect **deafness in infants**.
- In response to sound, **five distinct electrical potentials arising from different stations along the peripheral and central auditory pathway can be identified using computer averaging from scalp surface electrodes**—BERA.
- Principle: Sound in the cochlea (is converted into) electrical impulse that passes from cochlea to auditory cortex and produces various waveforms.

Indications

- For **detection of deafness** in difficult to test cases: like infants/mentally retracted or malingeringers
- For assessment of the **nature of deafness** (conductive or sensorineural)
- For **identification of the site of lesion in retrocochlear pathologies** (particularly acoustic neuromas)
- To study the **maturity of the CNS in newborns**
- For objective **assessment of brain-death** and for assessing prognosis in a comatose patients
- To diagnose **brainstem pathology** (ex: multiple sclerosis or pontine tumor)
- For **intraoperative monitoring**

Types of BERA waves

Wave I = Distal part of **E**ight nerve
 Wave II = Proximal part of **E**ight nerve
 Wave III = **C**ochlear nucleus/Lower pons
 Wave IV = Superior **O**livary complex
 Wave V = **L**ateral lemniscus
 Wave VI-VII = **I**nferior colliculus

Mnemonic = '**E-COLI**'

VESTIBULAR-EVOKED MYOGENIC POTENTIAL (VEMP)

- This (**VEMP**) test elicits a vestibulocollic reflex whose afferent limb arises from acoustically sensitive cells in the saccule, with signals conducted via the **inferior vestibular nerve**. VEMP is a biphasic, short-latency response **recorded from the tonically contracted sternocleidomastoid muscle in response to loud auditory clicks or tones**.
- VEMPs may be **diminished or absent in patients with early and late Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo, and vestibular schwannoma**. On the other hand, the threshold for VEMPs may be lower in cases of superior canal dehiscence and perilymphatic fistula.

ASSESSMENT OF VESTIBULAR FUNCTION

Vestibular Function Tests

Clinical tests	Lab tests
<ul style="list-style-type: none"> Fistula test Romberg test Hallpike maneuver (positional test) Spontaneous nystagmus Gait Past-pointing and falling 	<ul style="list-style-type: none"> Caloric test Electronystagmography Galvanic test Optokinetic test Rotation test Posturography

Clinical Tests of Vestibular Function

Fistula Test

- Principle:** In case of fistulous communication between middle ear and labyrinth, any pressure change in external auditory canal (produced by pressing tragus or by Siegel's speculum) will stimulate lateral semicircular canal thus producing nystagmus/vertigo.
- Positive fistula test:** It means labyrinth is functioning and a fistulous fistula communication is present between middle ear and labyrinth.
 - In erosion of lateral semicircular canal as in cholesteatoma
 - Surgically created window in the horizontal canal fenestration surgery
 - Abnormal opening in oval window—poststapedectomy fistula
 - Abnormal opening in round window
 - Hypermobile stapes footplate.

Negative Fistula Test

- In normals
- In dead labyrinth

Contd...

Negative Fistula Test

False positive (i.e. +ve fistula test without the presence of fistula—**Hennebert's sign**)

- Seen in: Congenital syphilis and Ménière's disease

False negative

(i.e. fistula is present but still test is -ve)

- When cholesteatoma covers site of fistula
- Ill fitting speculum

Romberg Test

- Proprioception** is the ability to sense the position of one's extremities without the aid of vision.
- The Romberg is a test of proprioceptive function:** It explores for imbalance due to proprioceptive sensory loss. The patient is able to stand with feet together and eyes open but sways or falls with eyes closed; it is one of the earliest signs of posterior column disease.

EXTRA EDGE

- Romberg's test is NOT a test of cerebellar function. Patients with cerebellar ataxia will generally be unable to balance even with the eyes open.

Conditions commonly causing a positive romberg test

- **Posterior column dysfunction:** Posterior cord compression; Multiple sclerosis; Subacute combined degeneration of the spinal cord; Tabes dorsalis
- **Sensory polyneuropathy:** Idiopathic; Diabetes mellitus
- **Intracranial lesions** (Less common)

Hallpike Maneuver (Positional Test)

- Particularly useful when patients complain of vertigo in certain head positions; **Helps to differentiate peripheral and central lesions**.
- Method:**
 - Patient sits on a couch. Examiner holds the patient's head, turns it 45° to the right and then places the patient in supine position so that his head hangs 30° below the horizontal. Patient's eyes are observed for **nystagmus**
 - The test is repeated with head turned to left
 - Four parameters of nystagmus are observed: Latency; Duration; Direction; Fatigability
 - Peripheral causes of BPPV can be differentiated from central causes (like tumors of IV ventricle, cerebellum, temporal lobe, multiple sclerosis, ↑ICV) by observing the characteristics of nystagmus.

Contd...

Nystagmus

Spontaneous nystagmus

- Nystagmus is rhythmic oscillatory movement of the eye.
- Nystagmus may be horizontal (side to side); vertical (up and down) or rotatory.
- Vestibular nystagmus has two components, slow and fast.
- The direction of nystagmus is indicated by the direction of the fast component.
- Vestibular nystagmus may be of 2 types:

1. Peripheral nystagmus

- Due to lesions of labyrinth or VIII nerve.
- Irritative lesions of the labyrinth (serous labyrinthitis) cause nystagmus to the side of lesion.
- Paretic lesions (purulent labyrinthitis, trauma to labyrinth, section of VIIIth nerve—cause nystagmus to healthy side.
- Peripheral nystagmus can be suppressed by optic fixation by looking at a fixed point, and enhanced in darkness or by the use of Frenzel glasses (+ 20 Diopters) both of which abolish fixation.

2. Central nystagmus

- Lesion is in the central neural pathways—vestibular nuclei, brainstem, cerebellum.
- Central nystagmus CANNOT be suppressed by optic fixation.
- Purely torsional nystagmus indicates lesions of brainstem/vestibular nuclei and is seen in syringomyelia.
- Acquired pendular nystagmus is seen in multiple sclerosis.
- **Downbeat nystagmus:** Lesions near the craniocervical junction (Chiari malformation, basilar invagination); Brainstem or cerebellar stroke; Lithium or anticonvulsant intoxication; Alcoholism; Multiple sclerosis.
- **Upbeat nystagmus:** Due to damage to the pontine tegmentum, or in lesions at the junction of pons and medulla or pons and midbrain.

	Peripheral Nystagmus	Central Nystagmus
Latency	2–20 seconds	No latency
Duration	< 1 minute	> 1 minute
Direction of nystagmus	Direction fixed toward the undermost ear	Direction changing
Position	Present in one head position	Present in multiple head positions
Vertigo	Always present	Occasionally present
Fatiguability	Fatiguable	Non-fatiguable
Symptoms	Severe vertigo	None or light

EXTRA EDGE

The cupulae of the semicircular canals are stimulated by movement of endolymphatic fluid and each canal causes the nystagmus in its own plane.

- Stimulation of **horizontal SCC—horizontal** nystagmus
- Stimulation of **superior SCC—Rotary** nystagmus
- Stimulation of **vertical SCC—Vertical** nystagmus

Lab Tests of Vestibular Function

Caloric Test

- **Principle:** To induce nystagmus by thermal stimulation of vestibular system. **Lateral semicircular canal** is commonly tested by all these tests. There are 3 methods of performing these tests.
 - **Cold caloric tests** with ice cold water modified (**Kobark's** test): Patient position: Patient is seated with head tilted 60°C backwards (to place horizontal canal in vertical position).
 - **Fitzgerald-Hallpike test (Bithermal caloric test):** Patient lies supine with head tilted at 30°C (so that horizontal canal is vertical). Ear is irrigated with water at 30°C and 44°C (body temperature ± 7°C).
 - In normal individuals, Cold water induces nystagmus to **Opposite** side and Warm water to **Same** side. (Mnemonic: **COWS**).
 - In case of dead labyrinth/canal paresis—no response/slow response.
 - **Cold-Air Caloric test by Dundas-Grant method:** Done in case of perforation of tympanic membrane (as irrigation with water is contraindicated in these cases); Air cooled by ethylchloride is blown into the ear by Dundas Grant tube.

Galvanic Test

- Galvanic test is the only vestibular test which helps in **differentiating an end organ lesion from that of vestibular nerve lesion.**

Optokinetic Nystagmus

- Patient is asked to follow a series of **vertical stripes on a drum** moving **first from right to left** and then from left to right.
- Normally it produces nystagmus with slow component in the direction of moving stripes and fast component is opposite direction.
- Optokinetic abnormalities are seen in brainstem and cerebral lesions. (central lesions)

DISORDERS OF VESTIBULAR SYSTEM

Benign Paroxysmal Positional Vertigo

- Characterized by vertigo when the head is placed in certain critical position.
- **Not a/w hearing loss** or any other symptom.
- Caused by disorder of **posterior semicircular canal** (debris is collected in it).
- MC in **5th decade**; H/O **head trauma/ear infections** may be present.
- **Vertigo is fatiguable** and may be a/w nausea.
- Characteristic nystagmus (latent, geotropic, fatigable) with Dix-Hallpike test.
- Management: **Vestibular exercises (Epley's maneuver, Cawthorne head exercises and Semont's maneuver)** done to reposition the debris in the utricle is the only current treatment of choice. In some patients' labyrinthine sedatives like prochlorperazine, promethazine may be given.
- In BPPV, **surgery** is reserved only for those very **rare** patients who have no benefit from vestibular exercises and have no intracranial pathology on imaging studies. Surgery of choice: **Posterior semicircular canal occlusion.**

Superior Canal Dehiscence Syndrome (SCDS)

- Vestibular symptoms are elicited by sound or pressure secondary to a dehiscence **superior semicircular canal.**
- The 2 windows of the inner ear work together to regulate hearing and balance. When a dehiscence in the superior semicircular canal is created, a '**third-window effect**' is thought to take place. As a result, endolymph within the labyrinthine system continue to move in relation to sound or pressure, which causes an activation of the vestibular system.
- M:F = 1:1; 4th decade affected.
- **Gait test:** normal; **Romberg test:** normal.
- **Fukuda test:** Patients who undergo this test are asked to step in place for 20–30 seconds with their eyes closed. Relation of the patient may indicate a unilateral loss of vestibular function. The results of this nonspecific test are typically normal in patients with SCDS.
- **Dix-Hallpike maneuver:** Patients with SCDS do not typically have positive Dix-Hallpike test results.

- **Head-shake test:** The results of this nonspecific test may be abnormal in patients with SCDS.
- **Head-thrust test:** The dynamic visual acuity test results are normal in patients with SCDS.
- **Fistula test:** It is positive when there is erosion of horizontal semicircular canal as in cholesteatoma or a surgically-created window in the horizontal canal (fenestration operation), abnormal opening in the oval window (post-stapedectomy fistula) or the round window (rupture of round window membrane).
- A **harany noise box** can be used to help elicit the noise-induced vertigo (Tullio phenomenon). This commercially available box simply makes a loud (**100 db**) noise. When the box is slowly moved towards the patient's symptomatic ear, the vertiginous symptoms may be recreated.

CONGENITAL HEARING DISORDERS

Autosomal Recessive

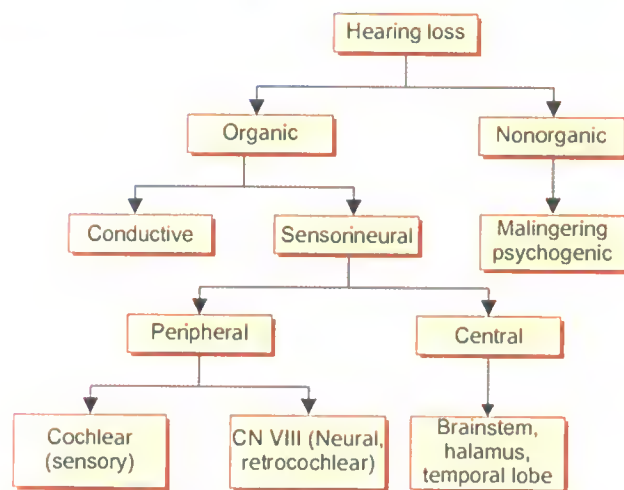
Pendred's syn.	Thyroid goiter and sensorineural hearing loss (SNHL)
Usher's syn.	Retinitis pigmentosa (RP) and SNHL
Jervell and Lange Nielsen syn.	Prolonged Q-T interval and SNHL
Refsum disease	RP, cerebellar ataxia, peripheral neuropathy and SNHL; accumulation of phytanic acid

Autosomal Dominant

Waardenburg's syn.	Telecanthus, pigment disorder (20% have a white forelock and 45% heterochromia iridis) with SNHL
Treacher-Collins syn.	Mandibulofacial dysostosis. microtia, external auditory canal atresia, malar and mandibular hypoplasia, antimongoloid slant of palpebral fissures, notched lower lids and atrophic lid margins
Pierre-Robin syn.	Hypoplastic mandible, cleft palate, glossoptosis. There may be external, middle or inner ear deformities
Crouzon's disease	Hypoplastic mandible and maxilla, parrot beak nose, craniosynostosis and exophthalmos with external and middle ear abnormalities
Apert's syn.	Congenital fixation of stapes footplate, acrocephaly, syndactyly, cleft palate, saddle nose

HEARING LOSS

Classification of Hearing Loss



Difference between Conductive and Sensorineural Hearing Loss

Features	Conductive	Sensorineural
Speech understanding	Good	Poor
Intolerance to loud sounds	Absent	Present in cochlear lesions
Speech of patient	Low voice	Loud voice
Paracusis willisii	Common	Absent
Common associated symptom	Otorrhea/earache	Tinnitus
Profound hearing loss	Never	Common
Rinne test	Negative (BC > AC)	Positive (AC > BC)
Weber test	Lateralized toward worst ear	Lateralized toward better ear
Absolute bone conduction	Normal	Reduced
Pure tone audiometry (PTA) Air Bone gap	Present	Absent
PTA: Recruitment	Absent	Present in cochlear lesions
PTA: Tone decay	Absent	Present in CN VII lesion
PTA: Frequencies	Usually low tones involved	Usually higher tones involved
PTA: Thresholds	Never > 60–70 dB	Can be > 60–70 dB
Speech discrimination	Not affected	Poor
Site of lesion	External and middle ear	Inner ear, CN VIII, central auditory connections

CONDUCTIVE HEARING LOSS

Hearing Loss in Conductive Defects

Complete obstruction of external auditory canal	30 dB
Malleus fixation	10–25 dB
Perforation of tympanic membrane (related to size of perforation)	10–40 dB
Ossicular interruption with perforation	38 dB
Ossicular interruption with intact drum	54 dB
Closure of oval window	60 dB

Surgeries for Treating Conductive Deafness

- **Tympanoplasty** = Repair of tympanic membrane (*myringoplasty*) + reconstruction of ossicular chain (*ossiculoplasty*). Types of *tympanoplasty* (*Wullstein*) is given under 'surgical management of middle ear suppuration' further down the chapter.

SENSORINEURAL HEARING LOSS

Difference between Cochlear and Retrocochlear SNHL

Cochlear SNHL	Retrocochlear SNHL
Hair cells are damaged mainly	Lesion is of VIII nerve or its central connections
Recruitment is present	Recruitment absent
No significant tone decay	Tone decay is significant
SISI (Short increment sensitivity index) is positive	SISI is negative
Bekesy audiometry shows no gap between I and C tracing (Type II)	Bekesy audiometry shows wide gap between I and C tracings (<i>type III</i>)
Speech discrimination is not highly impaired (SDS is low)	SDS very poor
Roll over phenomenon is not present	Roll over phenomenon is present
Subjective feeling of displacisus, hyperacusis or fullness in the ear	No such sensation or feeling

SPECIFIC FORMS OF HEARING LOSS

Presbycusis (Senile Deafness)

- **MC** cause of *sensorineural deafness*.
- Patient cannot tolerate high pitched voice and sound due to presence of recruitment.
- **Hearing aids** may provide limited rehabilitation once the word recognition score deteriorates below 50%.
- **Cochlear implants** are the treatment of choice when hearing aids prove inadequate, even when hearing loss is incomplete.

Noise Induced Hearing Loss

- Patients will have a typical notch (dip at **4 kHz, 4000 Hz**) in the audiogram called **acoustic dip**.
- Effects of noise exposure
 - **Auditory fatigue** occurs at **90 dB** and **greatest at 4000 Hz**.
 - **Permanent damage to hearing** (destruction of organ of Corti) occurs with repeated noise exposures to **100 dB**.
 - **Rupture of TM** may result from **noise > 160 dB**.
 - A **daily exposure of 85 dB** is the **maximum** that people can tolerate without substantial damage to their hearing.
 - A noise of **90 dB, 8 hours a day for 5 days** is the **maximum safe limit** as per **Factories Act**. No exposure in excess of 115 dB is permitted. No impulse of intensity > 140 dB is permitted.
 - Ear protectors (ear muffs or plugs) provide protection upto 35 dB.

Loudness

- Whisper = 30 dB
- Normal conversation = 60 dB
- Shouting = 90 dB
- Discomfort in the ear = 120 dB
- Pain in the ear = 130 dB

EXTRA EDGE

- **Hyperacusis**: 'Increased or painful sensitivity to everyday sounds that would not trouble a normal person'; It may involve malfunction of the **facial nerve (CN VII)**—hence the **stapedius muscle** is unable to dampen the sound.

Ototoxicity

- Clinical features of ototoxicity include: **sensorineural hearing loss**, tinnitus and vertigo.
- Among aminoglycosides, incidence of ototoxicity is **highest with neomycin** and **netilmycin is the weakest** ototoxic.
- Ototoxic drugs affect **higher frequencies (> 8000 Hz)** first—hence **high frequency audiometry** is done for monitoring.
- **Dihydrostreptomycin** has more selective effect on **cochlea** and **streptomycin sulfate** on the **vestibule**.

Ototoxic drugs	Examples	Site of action
Aminoglycosides	Mainly vestibulo-toxic: Streptomycin, gentamicin, tobramycin. Mainly cochleotoxic: Neomycin, kanamycin, amikacin, sisomicin	Destroy type 1 hair cells of the crista ampullaris

Contd...

Ototoxic drugs	Examples	Site of action
Vancomycin		Damage to cochlear hair cells initially of basal turn (high frequency)
Loop diuretics	Furosemide, ethacrynic acid	Edema and cystic changes in stria vascularis
Salicylates (Reversible)	Aspirin	Interfere at enzymatic level
Antimalarials	Chloroquine and quinine	Vasoconstriction in the small vessels of the cochlea and stria vascularis
Cytotoxic drugs	Nitrogen mustard, carboplatin, cisplatin	Affects outer hair cells
Iron chelating agent	Desferrioxamine	High frequency SNHL

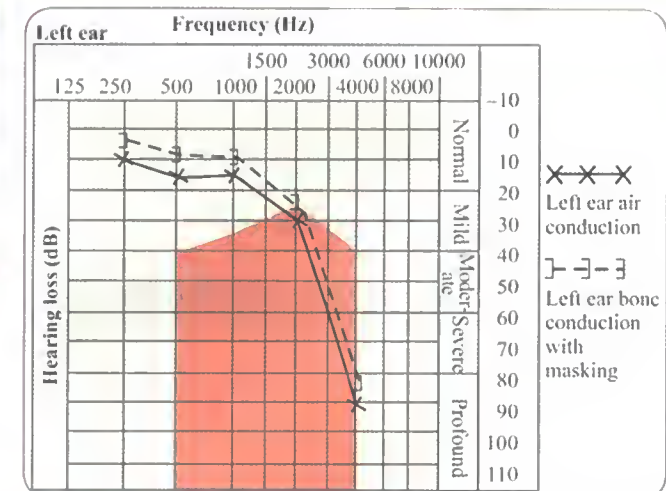


Fig. 18.22: Audiogram of a patient with ototoxicity. Bilateral symmetrical profound high-frequency SNHL

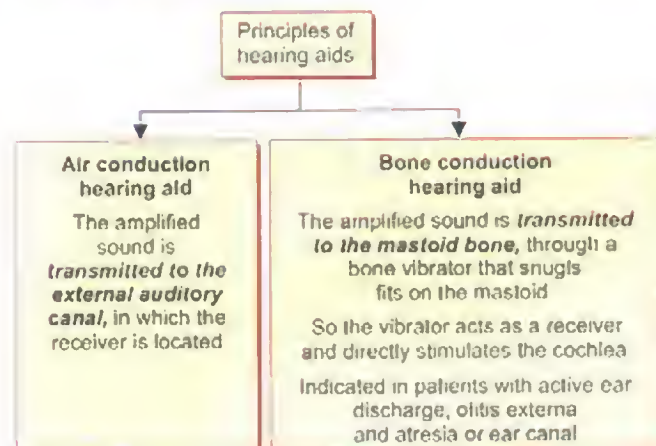
WHO Classification

Threshold dB in better ear	Degree of hearing impairment	Difficulty in hearing speech
0–25 dB	Not significant	Can hear faint speech
26–40 dB	Mild	Difficulty with faint speech
41–55 dB	Moderate	Difficulty with normal speech
56–70 dB	Moderately severe	Difficulty with loud speech
71–91 dB	Severe	Understand only shouted or amplified speech
> 91 dB	Profound	Cannot understand even amplified speech

Contd...

HEARING AIDS

Principle of Hearing Aids



Types of Hearing Aids

External hearing aids

- Body worn
- Behind the ear (BTE)
- Spectacle mounted
- In the ear (ITE)
- In the canal (ITC)
- Completely in the canal (CIC)

Implantable hearing aids

- Bone anchored hearing aid (BAHA)
- Implantable middle ear hearing aid:
 - Piezoelectric actuator
 - Piezoelectric sensor and actuator
 - Magnetic actuator

Disadvantages of BTE, ITE, ITC, CIC Hearing Aids

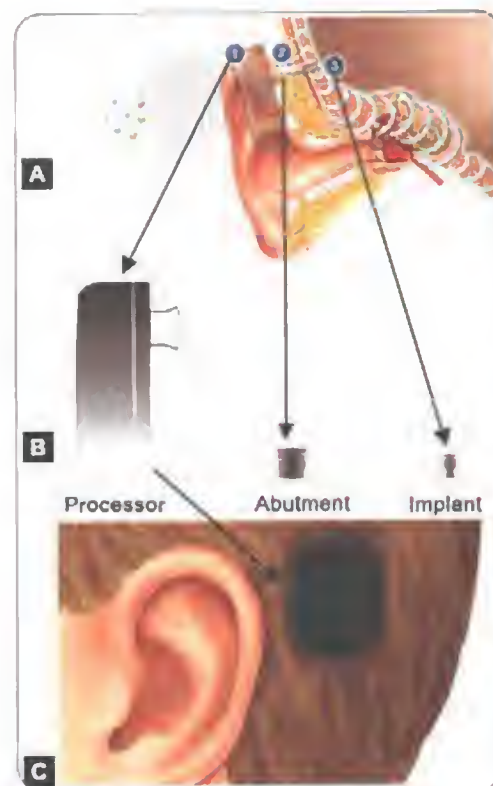
- **Acoustic feedback** (the amplified sound leaks from the receiver back into the microphone; creates high pitched squeal)
- **Spectral distortion** (low clarity of sound)
- **Occlusion of External Auditory Canal (EAC)**
- **Blockage of EAC** and insert by ear wax
- Not suitable in **discharging ears**.

Bone Anchored Hearing Aid (BAHA)

- Based on principle of bone conduction; it uses surgically implanted abutment to transmit sound by bone conduction directly to cochlea thus by passing the EAC and middle ear.

Parts of a BAHA are:

- **Titanium fixture** (surgically embedded in the skull) ossointegration takes 2-6 months
- **Titanium abutment**: Attached to the titanium fixture remains outside the skin
- **Sound processor**: After completion of ossointegration, it is attached to the abutment.



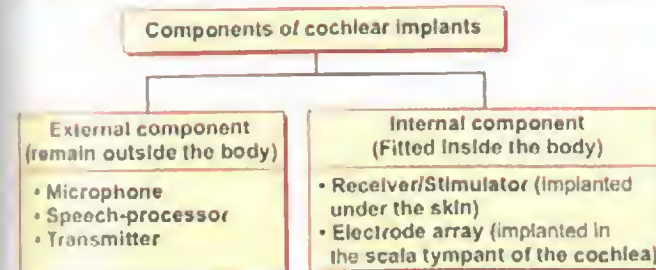
Figs 18.23A to C: BAHA: A. BAHA system; B. BAHA parts; C. BAHA processor in position

Source: Cochlear Limited

Indications for BAHA are:

- Chronic otitis media and otitis externa with **otorrhea** not amenable to treatment
- Congenital anomalies of ear (**anotia, microtia**)
- Canal **atresia**
- Otosclerosis and tympanosclerosis (when Sx is contraindicated and patient not willing for Sx)
- Unilateral profound hearing loss—single sided deafness (BAHA is implanted **on the side of hearing loss**; it transmits sound to normal side cochlea through bone conduction; this **eliminates head shadow effect**).

COCHLEAR IMPLANT



- It is an electronic device which converts **sound signal to electrical impulses** which **directly stimulate** the fibers of the **CN VIII**.
- Cochlear implants **replace the nonfunctional transducer system of hair cells** of cochlea.
- Used in **cochlear type of sensorineural hearing loss** where the nerve fibers remain intact and functional.
- The **electrodes are placed in the scala tympani of the cochlea** via a **cochleostomy** opening in the **basal turn of the cochlea** (after exposing the round window niche). The **electrodes stimulate the spiral ganglion cells (auditory nerve endings)** in the cochlea.

Outcomes

- Children and adults with postlingual short duration deafness achieve very good results
- If implanted early (**12 months of age**), even prelingual deafened children develop good understanding of speech and acquisition of language over a couple of years.

Also Know

Auditory Brainstem Implant (ABI) is indicated in cases of bilateral auditory nerve lesions (**bilateral acoustic neuroma as in NF-2**) when auditory nerve is cut during surgery. ABI **directly stimulates the cochlear nerve in the brainstem** and bypasses the auditory nerve.

EXTERNAL EAR DISEASES

Hematoma of Auricle

- Aka **cauliflower ear**
- Collection of blood between auricular cartilage and perichondrium; due to **repeated trauma** as in **boxers, wrestlers, rugby players**; treat with **aspiration** under asepsis with **prophylactic antibiotics**; if hematoma gets infected—severe perichondritis results.

Furuncle of External Canal

- **Staphylococcal** infection of **hair follicle in the cartilaginous part** of the meatus; pinna and tragus

are **tender, painful to insert a speculum**; periauricular lymph nodes may be enlarged and tender; early cases without abscess: Treat with 10% **ichthammol glycerine** pack; oral analgesics, oral antibiotics; If abscess formed: I and D done.

Diffuse Otitis Externa

- **Telephonauts ear, Singapore ear, Swimmer's ear**
- Seen in hot/humid climates; excess sweating changes the pH of the ear canal from acid to alkaline which favors growth of pathogens.
- Trauma is a predisposing factor.
- Common bacteria are *Staphylococcus aureus* and *Pseudomonas*.
- **Acute phase**: Hot burning in the ear which is aggravated by jaw movements; debris is collected and conductive hearing loss occurs; tender regional lymph nodes are seen.
- **Chronic phase**: Irritation and strong desire to itch. Scanty discharge.
- Rx with ear toilet, medicated wicks and antibiotics.

Malignant otitis externa

- Aka **necrotizing or invasive otitis externa**
- Occurs in **elderly uncontrolled diabetics, immunocompromised patients**
- Caused MC by *Pseudomonas aeruginosa*
- Presents as **dark purulent ear discharge** severe **deep seated otalgia**; MC nerve involved is VII (**facial**) nerve
- **Granulation tissue** at the bone-cartilaginous junction of posterior/inferior wall of external auditory canal seen
- Radionuclide scanning and **ESR** is used to monitor response to treatment
- High mortality rate
- Treat with aural toilet, systemic **antibiotics** (for **6-8 weeks**); **surgical debridement rarely needed**.

Otomycosis

- MC due to *Aspergillus niger*; external canal is filled with **wet debris or flakes resembling wet newspaper/ blotting paper**; musty odor; keep ear **clean and dry**; suction clearance; **antifungal** ear drops.

Bullous Myringitis

- A/w **influenza epidemic, mycoplasma, viral infections**; **hemorrhagic blebs** are found on the **tympanic membrane** and external canal; **painful**. After healing TM has '**sago-grain**' appearance.

Ramsay Hunt Syndrome

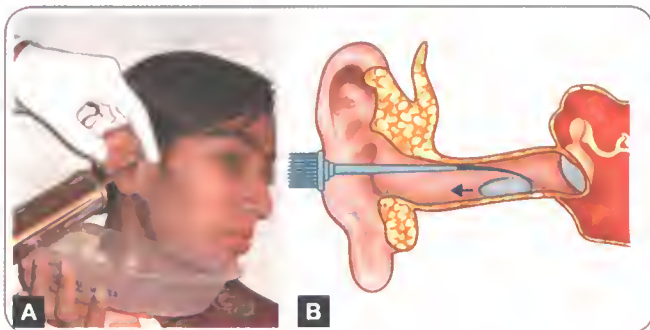
- **Herpes zoster infection of geniculate ganglion** leading to **LMN type facial palsy**; facial nerve has minor sensory supply in the **posteroinferior wall of the external canal**, which is evident by the appearance of herpetic eruptions.

Keratinosis Obturans

- External canal is filled with a mass consisting of *wax, desquamated keratinized epithelium, cholesterol simulating 'cholesteatoma' mass*. Chronic sinusitis and bronchiectasis are associated features.

Impacted Wax/Cerumen

- Causes itching, decreases hearing, tinnitus and vertigo; can try wax solvents like soda glycerine; if impacted and blocking view of tympanic membrane—**syringing**—with room temperature water—pull the pinna backwards and upwards and **direct jet of water along posterosuperior wall** of canal.



Figs 18.24A and B: Ear syringing: A. The auricle is pulled upwards and backwards and the direction of the ear syringe is posterosuperior; B. Water jet of ear syringe taking out lump of wax

Perichondritis of Pinna

- **MC** bacteria is **pseudomonas**; usually **secondary infection** from hematoma, lacerations etc.
- **Red, hot** and **painful** pinna with pus collection between cartilage and perichondrium.
- Rx with systemic antibiotics and drain the abscess.

Surfer's Ear

- **Surfer's ear** is the common name for an **exostosis** or **abnormal bone growth** within the ear canal.

Congenital Abnormalities of External Ear

Bat ear	MC congenital deformity of the pinna , an abnormal protrusion of the pinna with absence of antihelix ; usually bilateral; surgical correction after age of 6 years
Lop ear	The superior part of the pinna appears to be falling forwards ; more difficult to correct surgically
Darwin's tubercle	It is a small elevation on the posterosuperior part of the helix . This is an inherited condition and is homologous to the tip of the ear in mammals
Wildermuth's ear	The antihelix is more prominent than the helix. The lobule may be absent or adherent to the side of the head
Collaural fistula	These have an upper opening in the floor of the external auditory meatus and the lower opening behind the angle of the jaw at the anterior border of the sternomastoid . These skin tracts usually get infected and, are therefore treated by dissection of the tract and excision. The tract may lie deep to the facial nerve
Hereditary deafness	MC type is autosomal recessive (90%)
Accessory auricles	May be single or multiple presenting as skin tags; usually found in the preauricular region but may occur anywhere along a line extending down to the sternoclavicular joint. Excision for cosmetic reasons

DISEASES OF TYMPANIC MEMBRANE

Traumatic Rupture of Tympanic Membrane

- Etiology: Ear bud, pin injury or explosive blast or slap injury.
- Otoscopy shows **perforation of TM with irregular hemorrhagic margin**.
- Majority of cases heal with conservative treatment alone—**No eardrops** should be given. Healing of the perforation may be helped in some cases by application of trichloroacetic acid at the margin of the perforation.
- In majority of cases, the edges of the perforation get **inverted toward the middle ear**; in such cases, the ear should be examined under operating microscope and edges of perforation repositioned and splinted.

Retracted Tympanic Membrane

- Occurs as a result of **negative middle ear pressure** which occurs due to **blockage of Eustachian tube**.

Otoscopic signs are:

- ▶ Dull and **lusterless** TM
- ▶ **Absent** or interrupted cone of light
- ▶ Apparent **foreshortening** of handle of malleus
- ▶ **Extra prominent** lateral process of malleus
- ▶ **Sickle shaped** prominent anterior and posterior malleolar folds.

Grade's Grading of TM (Pars Tensa) Retraction

Grade	Title	Description
1	Retracted TM	Slight retraction of TM
2	Severe retraction	Retraction of TM with contact onto long process of incus
3	Atelectasis	TM touching promontory
4	Adhesive otitis	TM adherent to ossicles and promontory

Grade's Grading of TM (Pars Flaccida) Retraction Pockets

Grade	Description
1	Dimple or retraction of pars flaccida but NOT in contact with malleus neck
2	Pars flaccida retraction in contact with malleus neck
3	Erosion of scutum
4	Pocket with keratin (not self-cleaning) = cholesteatoma

DISORDERS OF EUSTACHIAN TUBE

Patulous Eustachian Tube

- **MC idiopathic**; **BUT** may be a/w in **third trimester of pregnancy**; **rapid weight loss** and **multiple sclerosis**.
- Here the patient hears their **own voice (autophony)** and **breath sounds**.
- A **benign** condition where the **eustachian tube** remains **abnormally open**.
- On otoscopy, one can see **movements of the TM that are synchronous with respiration**; the movements are exaggerated when patient breathes only through ipsilateral side of nose.
- Treatment: Weight gain; oral acetazolamide; cauterization of tubes; grommet insertion.

Tests for Eustachian Tube Function

Maneuver building positive pressure in nasopharynx

- Valsalva test (about 65% patients successfully perform this)
- Politzer test (good for children who cannot perform Valsalva test)
- Eustachian tube catheterization (used to relieve blockage of eustachian tube also)

Maneuver building negative pressure in nasopharynx

- Toynbee test (a physiological test where the patient is asked to swallow with his nose pinched; inward movement of TM can be seen with otoscope)
- Tympanometry (**best test**)

Tests for mucociliary clearance/drainage (done in cases of perforated TM)

- Saccharine
- Methylene blue
- Antibiotic/steroid ear drops

Sonotubometry

- Noninvasive test that provides information on active tubal opening; a tone which is delivered to the nose is recorded from external auditory canal—it is heard louder if Eustachian tube is open!

DISEASE OF MIDDLE EAR

Acute Suppurative Otitis Media (ASOM)

- **MC in children**; MC cause is **Streptococcus pneumoniae**. In neonates Group B Streptococcus and gram-negative bacilli predominate.

Stages of ASOM

- ▶ **Stage of tubal occlusion**
 - Blocked Eustachian tube leading to absorption of air and negative middle ear pressure with little effusion in middle ear
 - Mild deafness, ear ache; NO fever, **loss of cone of light (dull TM)** with prominence of lateral process of malleus
- ▶ **Stage of pre-suppuratation**
 - Bulging congested TM with **cartwheel appearance** (due to **leash of blood vessels** along the handle of malleus)
 - Marked ear ache, deafness, high fever present
- ▶ **Stage of suppuration**
 - Red bulging membranewith **nipplesign** and **lighthouseign**
 - Severe ear ache, deafness, high grade fever
- ▶ **Stage of resolution: TM ruptures** and pus drains out, middle ear dries and perforation heals

- Treatment: Clean ear discharge, oral antibiotics; **myringotomy (incision of TM curvilinearly in the posteroinferior quadrant** to drain out pus).
- **Recurrent otitis media**: Defined as either **3 bouts of ASOM in 6 months** or **4–5 bouts of ASOM in a year**. Causes may be allergy, chronic sinusitis, submucosal cleft palate, positive family history and nasopharyngeal carcinoma.

Secretory Otitis Media

- Also called **Glue Ear**; **Serous otitis media** or **otitis media with effusion**.

- **Eustachian tube dysfunction** (nasopharyngitis, hyperplasia of adenoids) leads to fluid collection in middle ear.
- **Hearing loss** leading to *inattentive behavior* and *turns up volume of TV!*, *fullness in ear*, minimal/absent pain.
- Otoscopy: ↓ mobility of TM, **fluid levels or air bubbles behind TM**, *straw or amber colored TM*.
- **Pneumatic otoscopy** is the **gold standard** for diagnosing glue ear; outward brisk movement of TM on reducing pressure in EAC with pneumatic otoscope.
- **Audiometry**—*conductive type* hearing loss in **20–30 dB** range.
- Impedance audiometry—**B type** of curve.
- X-ray—clouded mastoid air cells.

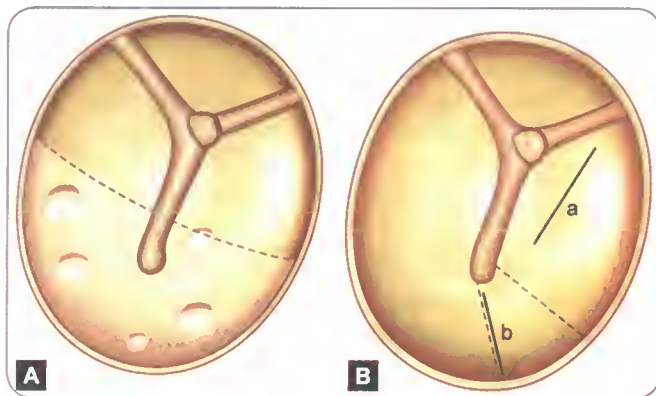
Medical Treatment

- Systemic **antibiotics**—efficacy of antibiotics has been shown by many reports.
- Nasal decongestants.

Surgical Treatment

- For persistent effusion (4–6 months) a/w hearing loss
- **Myringotomy with grommet insertion**
- Myringotomy with adenoidectomy

Remember! for persistent unilateral otitis media with effusion in adults; nasopharyngoscopy must be done to rule out Ca nasopharynx.



Figs 18.25A and B: A. Otitis media with effusion. Otoscopy shows fluid level and air bubbles; B. Incisions for middle ear effusion. **Key:** Two incisions: a. Anterosuperior quadrant and b. Anteroinferior quadrant

Acute Mastoiditis

- Occurs as *sequel to partial or untreated AOM in children*.
- Presents with **fever**, **retroauricular pain**, **sagging of skin of posterosuperior meatal wall**, **'ironed out' mastoid**, **tenderness over mastoid**.

- CT scan/X-ray shows clouding of mastoid air cells.
- Treat with **myringotomy and antibiotics**; if not resolved, **cortical mastoidectomy** needed.

Aero Otitis Media (Otitic Barotrauma)

- **Non suppurative** condition resulting from failure of Eustachian tube to maintain middle ear pressure at ambient atmospheric level.
- **BA**rotraumatic otitis media, trauma occurs during rapid **Descent ('BAD!')** during air flight or underwater diving.
- **Implosion injury: Slap injuries** and **explosions** also cause a type of barotrauma.
- When atmospheric pressure is higher than that of middle ear by critical level of **90 mm Hg**, Eustachian tube gets locked.
- Severe **ear ache**, **hearing loss (conductive)** and **tinnitus** are common; vertigo is **RARE**.
- TM appears retracted and congested and may rupture.
- Rx is by repeated swallowing and yawning/Valsalva maneuver; Eustachian tube catheterization or Politzerization; myringotomy in refractory cases.

Chronic Suppurative Otitis Media (CSOM)

CSOM is a longstanding infection (> **3 months**) of part or whole of the middle ear cleft. **MC** caused by *Pseudomonas aeruginosa*.

A chronically draining ear that fails to respond to appropriate antibiotic therapy should raise the suspicion of cholesteatoma.

Types of CSOM

Safe CSOM (tubotympanic)	Unsafe CSOM (atticoantral or tympanomastoid)
Copious discharge, odorless, intermittent, mucoid	Scanty foul (putrid) smelling continuous purulent discharge
Central perforation	Marginal or attic perforation
Granulations uncommon	Granulations common
Polyps are pale	Red and fleshy polyps
Cholesteatoma absent	Cholesteatoma present
Intracranial complications rare	Complications common
Treatment—conservative with aural toilet, eardrops, systemic antibiotics, myringoplasty	Treat with aural toilet, eardrops, systemic antibiotics, modified radical mastoidectomy

- In tubo-tympanic disease, sometimes patient reports a paradoxical effect, i.e. hears better in the presence of discharge than when the ear is dry - due to **'round window shielding effect'**.

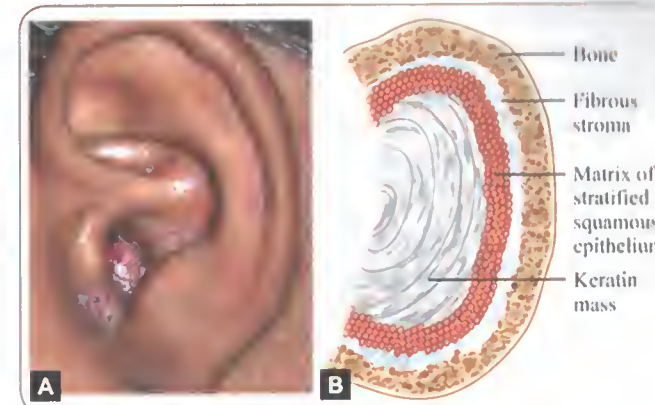
- **Pathology in attico-antral CSOM:**
 - Cholesteatoma
 - **Ossicular necrosis** (MC long process of incus)
 - **Cholesterol granuloma** (dark blue/black TM)
 - **Osteitis** and **granulation** tissue.
- Cholesteatoma has the property to **destroy bone** by virtue of the **enzymes** released by it. Structures immediately at risk of erosion are
 - Long process of incus
 - Fallopian canal of facial nerve
 - **Horizontal/lateral SCC.**
- Ear polyp is **NEVER** avulsed since it may be attached to the stapes, facial nerve and horizontal SCC and can injure these important structures.

Cholesteatoma

- Cholesteatoma—a **mishomer** since it is neither a tumor nor contains cholesterol!
- **Linings of middle ear cleft:**
 - Anterior and inferior part—ciliated columnar epithelium
 - Middle part—cuboidal epithelium
 - Attic—pavement like epithelium.
- Presence of **keratinizing squamous epithelium in the middle ear or mastoid** is called cholesteatoma (skin in the wrong place!).
- Cholesteatoma is seen in **sclerotic mastoid** and it is an **epidermal inclusion cyst**.
- **MC site** of origin is **posterior epitympanum**.

Classification of Cholesteatoma

- **Congenital cholesteatoma**
 - Arise from embryonic epidermal cell rests in the middle ear cleft
 - Sites: Middle ear, petrous apex, cerebellopontine angle.
- **Primary acquired cholesteatoma:** There is **NO** h/o previous otitis media, a pre-existing perforation or otorrhea.
 - **Retraction pocket theory (Wittmaack's theory):** ET obstruction > negative pressure in the middle ear cavity > formation of retraction pocket at the attic region > accumulation of desquamated epithelium > pressure necrosis of TM > cholesteatoma. A **posterosuperior retraction pocket** may progress to primary acquired cholesteatoma.
 - **Ruedi and Lange's theory: Basal cell hyperplasia**
 - **Wendt and Sade's theory: Squamous metaplasia.**
- **Secondary acquired cholesteatoma:** Occurs in **pre-existing perforation** of pars tensa of TM.
 - **Haberman's theory: Migration of squamous epithelium** of external canal into the middle ear cavity through the TM.



Figs 18.26A and B: A. A ear polyp; B. Cholesteatoma structure: stroma, matrix and keratin mass

COMPLICATIONS OF OTITIS MEDIA

Intratemporal	Extracranial
Within the temporal bone	Extradural abscess
• Mastoiditis	• Subdural abscess
• Petrositis	• Meningitis
• Facial paralysis	• Brain Abscess
• Labyrinthitis	• Lateral (sigmoid) sinus thrombophlebitis
	• Otitic hydrocephalus

- **MC complication of acute otitis media: Acute mastoiditis**
- **MC intracranial complication of acute otitis media and CSOM: meningitis**
- **MC extracranial complication of CSOM: Acute mastoiditis**

Acute Mastoiditis

- **MC** accompanies or follows acute suppurative otitis media especially in cases of measles, poor nutrition or diabetes.
- **MC cause** is beta hemolytic *Streptococcus*
- Two main pathologic processes are:
 - Production of pus under tension
 - Hyperemic decalcification and osteoclastic resorption of bony walls.
- Both above processes combine to cause destruction and coalescence of mastoid air cells, converting them into a single irregular cavity filled with pus (empyema of mastoid).
- Symptoms: Pain behind the ear; low grade fever; profuse purulent ear discharge.
- Signs
 - Mastoid tenderness with swelling over mastoid
 - Pulsatile ear discharge (lighthouse effect)
 - Sagging of posterosuperior meatal wall

- Perforation of TM—small perforation in pars tensa
- Conductive hearing loss.
- Treatment
 - Hospitalize and systemic antibiotics (amoxicillin + metronidazole).
 - Myringotomy
 - Cortical mastoidectomy in resistant cases.

Subperiosteal Abscesses

These occur as a complication of acute mastoiditis:

- **Postauricular: MC type**, Postauricular sulcus is deepened.
- **Zygomatic abscess**: Pus escaping from the zygomatic air cells forms abscess deep to the temporalis muscle and produces swelling above and in front of the ear and also edema of upper eyelid.
- **Luc's abscess**: Pus passes between the antrum and external osseous meatus.
- **Bezold's abscess**: Pus after erosion of mastoid tip or inner surface may give rise to an **abscess in the sternomastoid muscle** within its sheath.
- **Citelli's abscess**: Forms in the **digastric triangle** by breaking down of tip cells through the inner aspect of mastoid tip along digastric muscle.
- Pharyngeal abscess

Petrositis

- Infection of petrous part of temporal bone is petrositis.
- **Persistent ear discharge** in cases of *cortical or modified radical mastoidectomy* may be due to *petrositis*.

Gradenigo's syndrome

- Deep temporal **headache**
- **Retro-orbital pain**
- **Diplopia** (Paralysis of abducens nerve)

Sigmoid Sinus (Lateral Sinus) Thrombosis

- Hectic rise of temperature associated with rigor - '**picket fence**' fever (due to periodic release of hemolytic streptococci causing intermittent bacteremia in the blood). In between rigors patient looks surprisingly well and free from symptoms!
- **Griesinger's sign**—An indurated tender area over the upper part of the internal jugular vein and mastoid region may be palpated due to extension of thrombosis.
- **Tobey-Ayer test (Queckenstedt test)**—A lumbar puncture needle is introduced in the spinal canal and the needle is attached to a manometer and the effect of compression of jugular vein on each side is compared. When one vein is thrombosed, the compression of

the other causes much greater comparative rise in CSF pressure. Compression of the thrombosed side produces no increase at all.

- A **contrast-enhanced CT scan** is the **investigation of choice**—**Empty Delta sign** (enhancement of sinus wall but not contents).
- **Crowe-Beck test**: Pressure on jugular vein of healthy side produces engorgement of retinal and suprachoroid veins.
- **Headache, papilledema** and **tenderness along jugular vein** are seen.
- Treatment: IV antibiotics, mastoidectomy and exposure of sinus.

Otogenic Brain Abscess

- 50% brain abscess in adults and 25% in children are otogenic in origin.
- In adults it is common following CSOM whereas in children it follows acute otitis media.
- **Cerebral abscess** twice more common (than cerebellar)
- MC site of cerebral abscess is **temporal lobe**.
- **CT scan** is investigation of choice.
- Treatment: Parenteral antibiotics; dexamethasone or mannitol for raised ICT; neurosurgical drainage of abscess.
- Treat associated ear disease also.

EXTRA EDGE

- **Otitic hydrocephalus**: Rare finding, increased intracranial tension, but normal CSF findings.

SURGICAL MANAGEMENT OF MIDDLE EAR SUPPURATION

Incisions for Ear Surgery

- **Postaural** (William Wilde's) and **endaural** (Lempert's) incisions are used in *mastoidectomy* and *tympanoplasty*.
- **Endomeatal** (Rosen's) incision is used in stapedectomy and in tympanoplasty

Myringotomy

- Myringotomy was **first performed by Astley Cooper** for serous otitis media
- Incising the tympanic membrane to drain the middle ear
- Can be coupled with insertion tube (grommet).

Indications for myringotomy

- **Acute otitis media**.
- Otitic barotrauma for drainage and unblocking Eustachian tube.

Myringotomy is coupled with grommet insertion in

- Supportive or serous otitis media, recurrent acute otitis media, adhesive otitis media, ménière's disease.

EXTRA EDGE

- **Myringotomy is contraindicated** in case of suspected *Intratympanic glomus tumor*—in such a case tympanotomy should be done.

Preferred site for myringotomy

- In **Acute Suppurative Otitis Media** (ASOM); **circumferential** incision is made in the **posteroinferior** quadrant of tympanic membrane, midway between handle of malleus and tympanic annulus.
- In **Serous Otitis Media** ± grommet insertion, a small **radial** incision is given in **anteroinferior** quadrant.

Myringoplasty

- **Repair of tympanic membrane defect** (In Pars tensa)
- **MC graft** material used is **temporalis fascia**
- **Other materials** include tragal perichondrium, fat and vein (autografts), or cadaveric dura and vein (homografts)
- Indication is a **perforated tympanic membrane with only mild conductive hearing loss**, which implies a normal ossicular chain.

Tympanoplasty

- Eradication of disease from middle ear along with repair, which **includes ossicular reconstruction** with or without **myringoplasty**.
- Types of tympanoplasty: **Wullstein and Zollner** classification.

- | | |
|----------|--|
| Type I | Repair of perforated TM with a graft = myringoplasty |
| Type II | For TM perforation + erosion of malleus; graft is placed on the incus or remnant of malleus |
| Type III | Malleus and incus are absent; graft is placed directly on the stapes head—also called myringostapediopexy or columella tympanoplasty |
| Type IV | Only footplate of stapes is present; graft is placed between the oval and round windows (Baffle effect) |
| Type V | Stapes footplate is fixed, but round window is functioning; another window is created on horizontal SCC and covered with a graft (fenestration) |

EXTRA EDGE

- **Commonest ossiculoplasty material** is **autograft incus (incus transposition)**. Others are autograft tragal/septal cartilage, homograft ossicle and prosthetic materials. Prosthetic materials are made up of *Teflon, ceramic, titanium, gold*.

Cortical Mastoidectomy

- Aka **Simple mastoidectomy/Schwartz operation**.
- Involves **exenteration of all accessible mastoid air cells** without taking down the posterior meatal wall.
- Indications for cortical mastoidectomy
 - Acute coalescent mastoiditis
 - Incompletely resolved otitis media with **positive reservoir sign** (i.e. meatus immediately fills with pus after it has been mopped out).
 - Masked mastoiditis
 - As an initial step to perform endolymphatic sac surgery; decompression of facial nerve; translabyrinthine or Retrolabyrinthine procedure, for acoustic neuroma.

Radical Mastoidectomy

- Aims at exenteration and exteriorization. NO reconstruction is attempted.
- The disease from the middle ear and mastoid is exenterated, middle ear, attic, antrum and mastoid air cells are converted into a **single cavity by taking down the posterior canal wall** and thus exteriorized. The *whole mucosa of the middle ear, remnants of tympanic membrane, and ossicles except stapes* are removed. The middle ear is closed off by curetting the Eustachian tube and plugging with muscle. *NO attempts are made to preserve hearing*.
- Indications of radical mastoidectomy
 - **Malignancy** of the external ear and middle ear.
 - **Unresectable cholesteatoma**, scarring, Eustachian tube orifice, and producing severe sensorineural hearing loss.
 - If previous attempts to eradicate cholesteatoma have failed.

Modified Radical Mastoidectomy

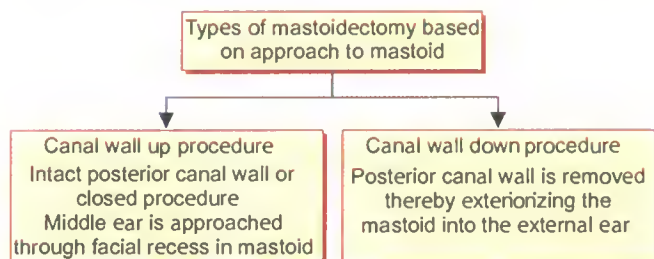
- Here in addition to exenteration and exteriorization, **reconstruction of the hearing mechanism is also attempted**. So in addition to creating an open cavity as in radical mastoidectomy *all healthy mucosa, remnants of tympanic membrane and ossicles are preserved to facilitate tympanoplasty later on*.
- This is the **treatment of choice for atticotympanic disease** and resectable cholesteatoma of middle ear and mastoid (localized chronic otitis media).

Methods to avoid injury to facial nerve during mastoidectomy

- Change to higher power of microscope near facial nerve
- Adequate irrigation to avoid thermal injury
- Avoid using cutting burr near the nerve (use diamond burr instead)
- Use the burr along the directions of the nerve—never across
- Never pull out granulations on the nerve

Note:

- **MC site of injury** to the facial nerve during **mastoidectomy** is the **2nd genu**



	Canal wall up	Canal wall down
Examples	Combined approach tympanoplasty Posterior tympanotomy	Radical mastoidectomy Modified radical mastoidectomy Bondy operation
Posterior canal wall	Not removed	Removed
Mastoid and ear canal	Remains separate	Merged with each other
Meatoplasty	Not required	Required
Postoperative regular cleaning under microscope	Usually not needed	Usually required
Rate of recurrence/residual cholesteatoma	High	Low
Second look surgery	Required after 6 months	Not required
Swimming	Allowed	Usually discouraged
Hearing aid fitting	Easy	Problematic

TUBERCULAR OTITIS MEDIA

- In **Tubercular otitis media** infection is carried up the Eustachian tube by infected cough particles
- MC secondary to pulmonary TB
- MC seen in children and young adults
- Painless necrosis of TM may be seen
- *Painless scanty, thin foul smelling otorrhea*

- **Multiple perforations** of the TM
- **Severe conductive** hearing loss out of proportion to symptoms
- **Facial palsy** is a common complication and may be the presenting feature in a child
- Treat with ATT.

OTOSCLEROSIS

Etiopathogenesis

- **AD, family h/o deafness** ++ in 70% cases; **common in South Indians and whites**; **M:F = 1:2** in **15–35 years age group**; **pregnancy** may initiate or aggravate otosclerosis
- Normal temporal bone has embryonic cartilage rests called **globuli interossei**—sites of predilection for otosclerosis.
- This is a disease of the bony labyrinth in which **vascular spongy bone formation** near the **oval window** causes **fixation or ankylosis of the footplate of the stapes**.
- **MC site** is **fissula ante fenestram** in front of the oval window.

Clinically

- **MC cause of non-suppurative conductive deafness in the adult.**
- Main symptom is **progressive deafness** usually **bilateral**. **Tinnitus** is present in **80%** cases.
- **Paracusis Willisii (Lombard effect)** is present—It is the ability to hear better in noisy surroundings as people talk louder in a noisy place.
- Otoscopy reveals normal intact and mobile tympanic membrane in most cases.
- In some (2%) cases **flamingo pink tinge** may be seen due to vascular otospongiotic mass and is called **positive Schwartze's sign**.
- Systemic associations: **Van der Hoeve's syndrome**—Otosclerosis with blue sclera and pathologic bone fractures; **Paget's disease**.

Methods to avoid injury to facial nerve during mastoidectomy

- **Rinne's test is negative** and **Weber is lateralized to the more affected ear** (conductive deafness); **Gelle's test is negative**; **Type A** or **Type A tympanogram**
- In **early cochlear otosclerosis**, **cookie-bite curve** shows that there is greatest degree of hearing loss in mid-frequency range.
- **Carhart's notch in BC at 2000 Hz** is present in some cases.
- Histologically—**first sign** is a change in the extracellular staining pattern—'**blue mantle**'; later 'otospongiosis' and finally 'otosclerosis'.

Treatment

- **Stapedectomy with artificial prosthesis** is the surgery of choice. Total or subtotal removal of stape footplate is stapedectomy; In stapedotomy a hole is made within the center of footplate of stapes (usually with laser). In stapedotomy, lenticular process of incus is left intact (structure cut are anterior and posterior crus of stapes and stapedius tendon).
- **Indications** for stapedectomy:
 - Firmly fixed staped as indicated by an air-bone gap of 30 dB
 - Negative Rinne for 256 and 512 Hz magnesium tuning forks
 - Speech discrimination score of 30% or more.
- **Hearing aids** that amplify the sound waves and this overcomes the resistance to sound transmission.
- **Cochlear otosclerosis** is treated by **Fluoride therapy**.

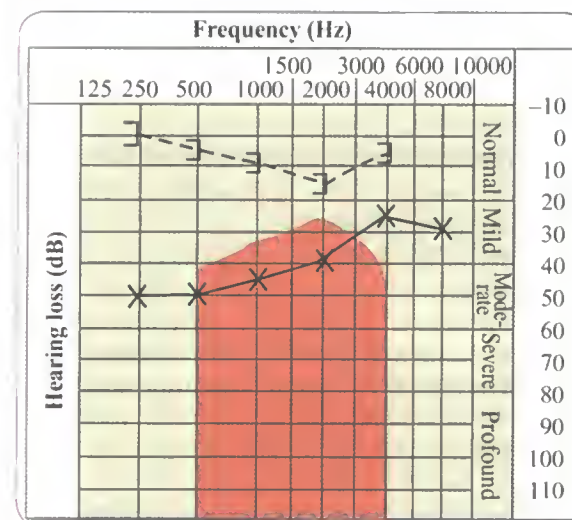


Fig. 18.27: Audiogram otosclerosis. Left ear predominantly low-frequency conductive hearing loss Carhart's notch

DISEASES OF INNER EAR

Meniere's Disease

Etiopathogenesis

- Aka **Endolymphatic Hydrops, Glaucoma of Ear, epileptiform cerebral congestion.**
- **Distension of endolymphatic system** due to **↑endolymph volume**: due to **faulty absorption** or **production** of endolymph or both.
- Other theories: **Vasomotor disturbance**; **sodium and water retention**; **allergy**, **hypothyroidism**; **autoimmune** and **viral etiologies**.

- **Schuknecht theory: Ruptures in the membranous labyrinth** allow leakage of **K⁺ rich endolymph** into the perilymph.

Clinically

- Usually **unilateral**; **F:M = 3:1**; affects **50–60 years age group**.
- Attacks of **episodic vertigo** (*first symptom*), **fluctuating sensorineural hearing loss**, **tinnitus** and **aural fullness**.
- **Diplacusis** (same sound perceived as different pitch in 2 ears); **music** appears **discordant**.
- **Intolerance to loud sound** due to recruitment phenomenon; hence **poor candidates for hearing aids**.
- **Hennebert's sign**: Vertigo and nystagmus experienced by patient during pressure induced excursion of the stapedial footplate (**false positive fistula test**)
- **Tulio's phenomenon**: Loud noise produces vertigo (**imbalance and nystagmus**) due to distended sacule lying against the stapedial footplate.

Tests in Meniere's disease

- **Tuning fork tests**: Sensorineural loss: Rinne test positive; absolute bone conduction is reduced in affected ear and Weber is lateralized to better ear
- Pure tone audiometry, **low frequency sensorineural hearing loss** present (**raising type curve**); with progressive disease curve becomes flat or falling type (B or C)
- **Recruitment is positive**; **High SISI (short increment sensitivity index)** score > 70% (N<15%); **Tone decay test**—normally there is little decay of < 20 dB
- On **electrocochleography**, Summating Potential (SP): Action Potential (AP), i.e. **SP:AP (> 30%)** is **diagnostic**
- **Elevated VEMP** (vestibular evoked myogenic potential) thresholds with flattened tuning
- **Caloric test: Show canal paresis** (reduced response on affected side)
- **Glycerol test**: When glycerol is given orally, it reduces endolymph pressure and causes and improvement in hearing.
- 'Cochlear hydrops analysis masking procedure (**CHAMP**)'—EEG response measured during presentation of clicking sounds to the ear.

Treatment

- General measures: Low salt diet, stop smoking (nicotine causes vasospasm); **AVOID** excess water/coffee/tea/alcohol and stress.
- **Acute attack**: Bed rest; vestibular sedatives (**dimenhydrinate, promethazine, prochlorperazine**); vasodilators (inhalation of **carbogen**—5% CO₂ with 95% O₂); **hista-**

mine drip—contraindicated in asthmatics and empty stomach.

- **Chronic phase:** Vestibular sedatives, vasodilators (nicotinic acid, betahistine); diuretics (furosemide), propantheline bromide.
- **Surgical treatment:** When all else fails.

Hearing-conservative nonvestibular ablative surgery:

- **Decompression of endolymphatic sac;**
- **Endolymphatic shunt** operation;
- **Sacculotomy** (Fick operation and **Cody's** tack procedure);
- **Cochleosacculotomy;**
- **Transtympanic corticosteroid** infusion into middle ear.

Hearing-conservative vestibular ablative surgery:

- **Vestibular nerve sectioning;** Ultrasonic destruction of vestibular labyrinth.
- **Chemical labyrinthectomy** (intratympanic gentamicin) destroys vestibular labyrinth—vestibulotoxic; medication delivered to labyrinth by **Silverstein Microwick and Microcatheter**; gentamicin acts by destroying the 'dark cells' (melanoreceptors) of the secretory epithelium, thus decreasing endolymph production.
- Cryosurgery, cochlear dialysis.

Non-hearing conservative vestibular ablative surgery (destructive procedures)

- **Labyrinthectomy**
- Translabyrinthine cochleovestibular neurectomy
- Destruction of Scarpa's ganglion

Others

- **Intermittent low pressure pulse** therapy (**Meniett device**); a prerequisite is to do a myringotomy and put a ventilation tube so that the device when coupled to the external ear canal can deliver pressure waves to the round window membrane via the ventilation tube.

Variants of Ménière's

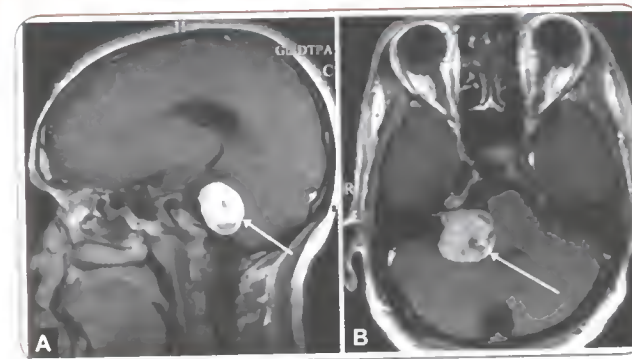
- **Lermoyez syndrome** = symptoms of Ménière's in reverse order; first deterioration of hearing is seen and SNHL improves suddenly during attacks of vertigo.
- **Cochlear hydrops** = only cochlear symptoms are present, NO vertigo.
- **Vestibular hydrops:** Only vestibular symptoms; cochlear function normal; also called 'recurrent vestibulopathy'.
- **Otolithic Crisis of Tumarkin** = sudden 'drop attacks': Patient loses his extensor powers and falls to the ground during a sudden, severe, and short episode of vertigo; completely conscious throughout this episode and recovers promptly afterwards.
- **Ménière's syndrome: Secondary Ménière's disease;** may be due to head trauma, ear surgery, virus (mumps, measles), syphilis, Cogan's syndrome, otosclerosis or autoimmune disorders.

ACOUSTIC NEUROMA (VESTIBULAR SCHWANNOMA)

- Benign slow growing tumor that arises from the **neurilemmal sheath** of the **intracanalicular portion** of **inferior (MC)** or **superior vestibular N** at the transition zones (**Obersteinerredlich zone**) of central and peripheral myelin, i.e. where the glial cells are replaced by Schwann cells.
- **MC (80%) of all CPA angle tumors;** age group 40–60 years (Note: II MC CPA tumor is **meningioma**).
- **MC unilateral (90%); bilateral** acoustic neuroma is diagnostic of **Neurofibromatosis-2 (NF-2)**.
- Early symptom is **unilateral sensorineural deafness (MC) with tinnitus**.
- In advanced cases **CN V is involved first** (↓ corneal sensation and reflex, **MC presenting sign**), followed by CN 7 and CN 3.
- **Hitzelberger's sign:** Hypoesthesia of posterior wall of external auditory canal, because of facial nerve (CN 7) involvement
- **Treatment:** Microsurgery is treatment of choice; more incidence of facial nerve damage, BUT preserves hearing
 - **Retrosigmoid (suboccipital):** It can be used for large tumors
 - **Middle cranial fossa approach—best for small intracanalicular tumors**
 - **Translabyrinthine approach:** It causes **sensorineural hearing loss**.
- **Other modalities:** Observation only (for small non progressive tumors); **External beam radiotherapy; Stereotactic radiosurgery** (Gamma knife, cyberknife, linear accelerator); Fractionated stereotactic radiotherapy, **Bevacizumab** (in bilateral VS a/w NF-2).

Investigations in acoustic neuroma

- X-ray of internal auditory meatus may show expansion and erosion of canal
- Audiometry shows '**dip**' in **audiogram** at **4000 Hz** (downsloping high frequency hearing loss)
- **Speech discrimination is poor**
- **Roll over phenomenon is present.** (Patient's speech discrimination is worse than expected based on pure tone averages that become worse as the sound is intensified)
- **Recruitment absent**
- Threshold tone decay test shows **retrocochlear type** of lesion
- **BERA** (Brainstem Evoked Response Audiometry): Delay of > 0.2 ms in wave V between 2 sides
- **MRI with contrast is gold standard** for imaging. (widening of the porus acousticus results in the '**trumpeted internal acoustic meatus**' sign); '**Ice cream cone**' sign may be seen
- Histology—Spindle cells of **Antoni type A (verocay bodies)** or **Antoni type B**



Figs 18.28A and B: MRI of brain with gadolinium contrast in a case of CPA tumor: A. Sagittal section; B. Axial section (arrows showing)

Source: Dr Ritesh Prajapati, Consultant Radiologist, Anand, Gujarat

GLOMUS JUGULARE/TYMPANICUM TUMORS

- Aka **chemodectomas, nonchromaffin paragangliomas**.
- **MC benign neoplasm of middle ear.**
- Actually, '**glomus**' is a **misnomer** because these **glomus bodies** derive from **neural crest** elements that are felt to migrate with **sympathetic autonomic ganglion cells** to **form paraganglia**.
- **Glomus tumors** also found in the **adrenal** and **extra-adrenal** systems BUT in the temporal bone they are **nonchromaffin** (i.e. **lack affinity for chromium salts** on histology analysis).
- In the temporal bone, glomus tumors
 - **Arise from dome of jugular bulb, (glomus jugulare) or in**
 - **Promontory of middle ear (glomus tympanicum)**
- Glomus tumors also occur in the **carotid body** and the **vagus nerve**.
- MC site in middle ear is **hypotympanum**.
- **Highly vascular** tumor with **ascending pharyngeal artery** being main blood supply.
- Histologically **clusters of chief cells called Zellballen** are seen.
- **Clinically**
 - Present between 40 and 70 years of age; **female preponderance** of between 3:1; more commonly occurs on the **left side**;
 - Commonest symptoms are **deafness** and a **pulsatile tinnitus**; pain in the ear is uncommon;
 - **Auscultation** over the mastoid or infraauricular region may appreciate a **bruit (objective tinnitus)**.
- The MC used classifications are **Glasscock-Jackson** and **Fisch**.
- **Rule of 10's:** 10% are familial; 10% are multicentric and 10% functional (i.e. secrete catecholamines).

Signs in glomus tumors

- There may be otorrhea, hemorrhage and the presence of a middle ear mass; otoscopic examination reveals a characteristic, pulsatile, reddish-blue tumor behind the intact tympanic membrane—'**red drum**'.
- '**Brown's sign/Pulsation sign**': On application of pressure to the external ear canal with the help of a pneumatic ear speculum the mass could be seen to **blanch**.
- '**Aquino sign**' is the observation of **decreased pulsations with carotid compression**.
- '**Rising sun**' on **otoscopy**: When tumor arises from the floor of the middle ear.

Syndromes a/w glomus tumors

- If the **jugular foramen syndrome** develops (paresis of cranial nerves IX, X, XI), there may also be complaints of hoarseness, dysarthria, dysphagia or shoulder weakness (**Vernet syndrome**)
- The addition of Horner syndromic findings such as miosis, ptosis, and anhydrosis would suggest compression of the cervical sympathetic chain that constitutes **Villoret syndrome**.

Investigations

- Plain skull X-rays may show evidence of the lesion with enlargement of the lateral jugular foramen and fossa.
- **MRI shows 'salt and pepper' appearance** on T1 and T2 images.
- The best imaging technique is **CT combined with MRI with DTPA enhancement**.
- CT helps to assess the bony partition between the jugular fossa and hypotympanum; specifically, a **glomus jugulare often erodes the caroticojugular spine (Phelp sign)**; while a **glomus tympanicum** occupies the middle ear with general preservation of the bony partition.
- Positive on **octreotide scintigraphy**.
- Arteriography may be required before resection of large tumors.
- There should be screening for catecholamines.
- NEVER do a biopsy; very vascular tumor.
- **Treatment**
 - **Surgical resection** is the **treatment of choice**
 - **Embolization, radiotherapy, stereotactic (gamma knife) radiosurgery** and intratumoral injection of cyanoacrylate glue are other options.
- **Complications of glomus tumor:** Hearing loss (conductive; hypoglossal N palsy; facial N palsy (MC cranial nerve involved); ipsilateral Horner syndrome; jugular foramen syndrome.

RADIOFREQUENCY

- Radiowaves have been used surgically to **reduce the volume of tissues** and also to **cut and coagulate** tissues.
- Radiofrequency device generates electromagnetic waves—**460 kHz** is MC used.
- They have been used
 - On inferior turbinates to relieve nasal obstruction
 - On soft palate to relieve primary snoring, upper airway resistance and sleep apnea
 - On the base of tongue to relieve sleep apnea
 - Radiofrequency has also been used to perform (using special electrodes) tonsillotomy, microlaryngeal surgery, myringotomy, uvulopalatoplasty, correction of rhinophyma and cosmetic removal of skin lesions.

Lasers in ENT

- Lasers are used for microsurgery of the ear and larynx.
- Argon laser (488–514 nm)
 - KTP-532 laser
 - Nd:YAG laser (1060 nm)
 - **CO₂ laser** (10600 nm)—**MC** used laser in ENT.

MORE ONE-LINERS IN EAR

- **MC malignant** tumor of the **pinna** is **SCC**.
- Long standing middle ear suppuration is a predisposing factor for SCC.
- **Narrowest part of the facial canal** is 4 mm above the stylomastoid foramen.
- Sound **travels at** 760 miles/hour or 1100 feet/sec.
- **Most common** benign tumor of external canal is bony exostosis of the external canal.
- Maggots in the ear is called **Myiasis**.
- **Embryonal Rhabdomyosarcoma (ERMS)**—It is a highly invasive mesenchymal tumor occurring in young children and is usually fatal. Arises from undifferentiated and unsegmented mesoderm in middle ear and mastoid.

- **Posterior inferior cerebellar artery thrombosis** (lateral medullary syndrome; Wallenberg syndrome)—Severe vertigo occurs with ipsilateral cerebellar signs, Horner's syndrome and contralateral hemiplegia. Deafness may or may not be present.
- In **Vestibular neuronitis** (Viral infection of vestibular N), hearing remains normal.
- **Citelli's angle** is **sino-dural angle** (angle between the plate of bone separating the sigmoid signs from the mastoid cavity (dural plate)—a common site of residual/recurrent disease after surgery.
- **Oscillopsia** is a visual disturbance in which objects in the visual field appear to oscillate.
- **Habenula perforata**: The openings through which branches of cochlear nerve enter the cochlea; if wide it can lead to **perilymph gusher** in stapes surgery.
- **Complete absence of bony and membranous labyrinth** occurs in **Mondini's aplasia**.
- **Frey's syndrome**—**gustatory sweating** (sweating while eating) follows injury to **auriculotemporal nerve**.
- **Delphic nodes** are pretracheal lymph nodes.
- **Sade's classification** is for 4 stages of **tympanic membrane retraction**.
- Father of **Neurotology**: **Dr William F House**.
- **Lyre's sign**: Splaying apart of internal and external carotid arteries by carotid body tumor seen on carotid angiography.
- Viral infections causing hearing loss are **mumps** (due to involvement of labyrinth), **rubella**, **measles** and **herpes**.
- In **Viral** (Measles, Mumps, Influenza) **labyrinthitis**, sensorineural deafness is **severe and permanent**.
- As per **Cremier's classification** of congenital anomalies of the ossicular chain:
 - **MC type** is stapes ankylosis with another congenital ossicular chain anomaly.

NOSE

ESSENTIAL ANATOMY OF NOSE

- **Shape**: **Pyramidal** in shape and divided into 2 parts by the nasal septum.
- **Nasal septum**: It is made of **perpendicular plate of ethmoid** above and behind, **vomer** below and behind, **quadrilateral or septal cartilage** anteroinferiorly.

High yield MCQ area of nose

- **Lateral wall of nose**: Has 3 turbinates (conchae)—**Inferior Turbinate is a separate bone (IT's separate!)**; **middle** and **superior** turbinate are **part of ethmoid** bone; sometimes a fourth (**supreme**) turbinate is present above superior turbinate.

High yield MCQ area of nose

- **Inferior meatus**: Receives the **Nasolacrimal Duct**; (**INDia**); largest meatus.
- **Middle meatus**: Receives **FR**ontal sinus, **A**nterior and **M**iddle **E**thmoid sinus. Hiatus semilunaris receives **Maxillary** sinus; (**FRAME-M**).
- **Superior meatus**: Receives **P**osterior **E**thmoid sinus.
- **Sphenoethmoidal recess**: Receives the sphenoid sinus.

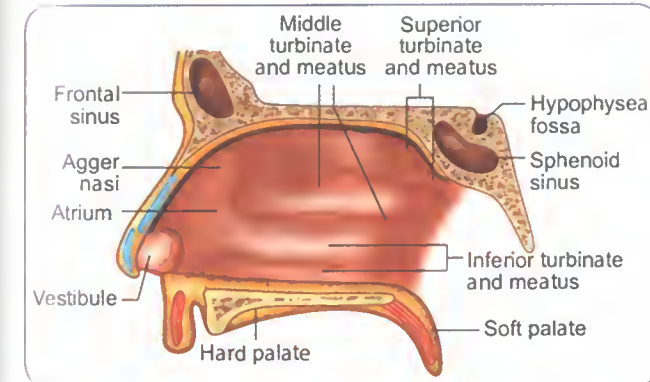


Fig. 18.29: Lateral wall of nasal cavity showing turbinates and meatuses

- **Hasner's valve**: Mucosal flap at distal end of **nasolacrimal duct**.
- **Osteomeatal complex area (Picadli's circle)**: It is that area of the middle meatus where the sinus ostia open and is an important **site of pathogenesis in sinusitis**.
- **Concha bullosa**: Pneumatization of middle turbinate.
- **Dangerous area of face**: Area around the nose, vestibule and upper lip is dangerous as infection from these areas may drain into **cavernous sinus** via **anterior facial and angular veins**.
- The **nasion** is the **intersection of the frontal and two nasal bones of the human skull**.

ABOUT PARANASAL SINUSES

Sinus	At birth	Adult size	X-ray appearance
Maxillary	Present	15 yrs	4–5 months
Ethmoidal	Present	12 yrs	1 year
Sphenoid	Absent	12–15 yrs	4 years
Frontal	Absent	13–18 yrs	6 years

- **Development of sinuses**: Order is **Maxillary** (1st to develop), **Ethmoid**, **Sphenoid**, **Frontal**. ('My Elite Security Force').
- **Maxillary sinus**: Aka **Antrum of Highmore**; largest paranasal sinus with an adult capacity of **15 cc**.

Cells associated with sinuses

- **Agger nasi cells**: Most anterior of **Anterior** ethmoidal cells and lie close to frontal recess; **can obstruct frontal sinus drainage**.
- **Haller cell**: **Anterior** Ethmoidal cell in roof of maxillary sinus/floor of orbit. **Haller cells overlooked during surgery** can be a source of **persistent mucopurulent secretion**.
- **Onodi cell**: **PO**sterior ethmoidal cell related to optic nerve; **identify these cells during FESS** to avoid **optic N injury**.

CHOANAL ATRESIA

- Choanal atresia occurs due to **persistence of the primitive bucconasal membrane**.
- **Bony atresia is more common** (90%) than membranous atresia; **Unilateral atresia is more common** than bilateral.
- Symptoms of severe **airway obstruction** and **cyclical cyanosis** are the classic signs of neonatal **bilateral atresia**—a **life-threatening condition**.
- **Unilateral** choanal atresia presents with **unilateral nasal obstruction and mucoid rhinorrhea**.
- Diagnosis is by
 - Presence of **mucoid discharge in the nose**
 - **Absence of air bubbles** in the **nasal discharge**
 - **Inability to pass a nasogastric tube into the nose** of a newborn with **presence of air in the lower respiratory tree**.

ACUTE SINUSITIS

Etiology

- **Streptococcus pneumoniae** (MC), **H Influenzae**, **M catarrhalis**.
- Sinuses involved in the following order: **MAXillary** > **FR**ontal > **E**thmoid > **S**phenoid (**MAX FRIES**).

Signs associated with sinusitis

- **Maxillary sinusitis**—**maxillary tenderness**, fever, bodyache, headache, postnasal drip
- **Frontal sinusitis**—frontal tenderness, **office headache**, increases during mid-day and decreases by evening (**periodicity of headache**), **vacuum frontal headache** due to blockage of frontonasal duct and absorption of air.
- **Ethmoid sinusitis**—**MC in young children**; **orbital cellulitis** is a complication **MC due to ethmoid sinusitis**
- **Sphenoid sinusitis**—**Severe retroorbital headache** (vertical headache), **postnasal drip**.

Imaging

- **Plain CT scan without contrast** is the first line screening study of nose and paranasal sinuses.
- **X-ray: Water's view** is a **submento occipital view** useful for most sinuses, except posterior ethmoids; **Caldwell's view** for frontal sinus; **Basal view** for posterior ethmoids and sphenoid.
- **Transillumination test** was used earlier for maxillary sinusitis—absence of intraorbital crescent of light and pupillary glow.

Treatment

- NSAIDs, antibiotics, steam inhalation.

Complications

- **Pott's puffy tumor** (Osteomyelitis of the frontal bone) and mucocele are complications of frontal sinusitis.

EXTRA EDGE

- **Acute rhinosinusitis** is sinusitis < 4 weeks duration; **chronic sinusitis** is > 12 weeks duration.

ATROPHIC RHINITIS

Etiology

- **Hereditary**; **Endocrine** (starts at puberty, stops after menopause); **Racial** (MC in yellow and white races); **Nutritional deficiency** (vitamin A, D, E, iron); **Infective** (*Klebsiella ozaenae* (Perez bacillus), *P. Vulgaris*, *E. coli*, *Staph* and *streptococci*); **Autoimmune** (autoantibodies destroying nasal mucosa). ('**IIERNIA**').
- **Secondary atrophic rhinitis**—Due to surgery (excessive resection of turbinates); trauma, infection, granulomatous diseases (syphilis, lupus, leprosy); radiation exposure.
- Primary atrophic rhinitis is common in India, China, Eastern Europe, Greece.

Pathology

- Ciliated columnar epithelium is lost and replaced by stratified squamous epithelium. Atrophy of seromucinous glands, **obliterative endarteritis** causing resorption of turbinates.

Features of atrophic sinusitis

- Most characteristic symptom is the **faul adar** detected by others while the patient himself/herself is anosmic ('**merciful anosmia**').
- **Raomy nasal cavities**, but nasal obstruction due to crusting
- In severe atrophic rhinitis when there is extensive crusting and fetor, the condition is known as **azaena**.

Treatment

- Medical
 - **Alkaline nasal douches**
 - 25% glucose in glycerine
 - **Estradiol** nasal spray
 - **Human placental extract**
 - **Kemicetine anti-ozaena solution** (chloramphenicol, estradiol and vitamin D2)
 - **Potassium iodide** to promote and liquefy nasal secretions
 - Oral streptomycin (for klebsiella)
- Surgical
 - **Young's operation** consists of closure of the anterior nares or narrowing of the anterior nares (modified Young's)
 - **Lautenschlager's operation** aimed at medializing the lateral nasal wall by submucous injection of paraffin
 - **Wilson's operation** (submucous injection of 50% teflon in glycerine paste).

Chronic diseases of nose

- **Nasal Syphilis: Congenital** syphilis: coryza (snuffles) characterized by obstinate nasal discharge and nasal crusting; fissuring of the anterior nares; **saddle nose**. **Acquired** syphilis: mucous patches in the nose, gumma in tertiary syphilis; **nasal septal perforation (BONY part)**.
- **Leprasy: Saddle nose, nasal septal perforation** (cartilaginous part); nodule formation over nasal septum
- **TB: Tuberculoma, lupus vulgaris** (apple jelly nodules on diascopy)
- **SLE: Ala of nose involved, nasal septal perforation** (cartilaginous part)

RHINOSPORIDIOSIS

Etiology

- Fungus **Rhinosporidium seeberi** (NON-cultivable fungus); common among **farmers, country dwellers**, MC in **southern India, Sri Lanka** and **Pakistan** predisposed by trauma; **acquired** through dust from dung of infected cattle and horses and through contaminated water of ponds.

Clinically

- Infects **MC, the nasal mucosa**, but extra nasal sites such as conjunctiva, skin, genitals, ear, etc. may be involved.
- Presents as **bleeding polyps** resembling **strawberry** with **white dots** representing sporangia.

Treatment

- Surgery—**complete excision of mass** with cutting diathermy and cauterization of its base. **Dapsone** has been tried.

RHINOSCLEROMA

Etiology

- Aka '**woody nose**'; A chronic granulomatous disease of the nose and respiratory tract caused by **Klebsiella rhinoscleromatis** (*Frisch bacillus*, gram negative); **common in North India**.

Pathology

- Granulation tissue consists in submucosa consisting of plasma cells, lymphocytes, **large foam cells** (**Mikulicz cells**) and **Russell bodies**.

Clinically

- Has 3 stages: catarrhal, atrophic stage, granulomatous stage (woody feel of upper lip and nasal vestibule) and cicatricial stage (**tapir nose**).

Treatment

- Drug of choice is **streptomycin/tetracycline**; radiotherapy is **NOT** effective.

NASAL POLYPS

Antrochoanal polyps	Ethmoidal polyps
<ul style="list-style-type: none"> • Due to infections • Solitary, trilobed with antral and choanal parts, common in children • Arises from maxillary sinus near the ostium • Unilateral, grows backwards to the choana, may hang down from behind the soft palate • Recurrence uncommon if removed completely • FESS (Fiberoptic endoscopic sinus surgery) is treatment of choice Other methods: Caldwell-Luc operation - Transantral ethmoidectomy (maxillary antrum opened through canine fossa and diseased mucosa removed) 	<ul style="list-style-type: none"> Due to allergy, vasomotor, a/w asthma Multiple, small grape like, common in adults (30–60 years) Arises from ethmoidal sinus Bilateral, grows anteriorly, may be seen at the anterior nares Recurrence common Treatment is mainly medical (intranasal corticosteroids) If surgical Rx, FESS is treatment of choice

EXTRA EDGE

- Topical corticosteroids (nasal sprays) are **NOT used in antrochoanal polyps** postsurgery (since cause is infective). However it is used for ethmoidal polyps; chronic rhinosinusitis and allergic fungal sinusitis.

CSF RHINORRHEA

Etiology

- Traumatic: **MC cause** is accidental **head injury**; due to **traumatic fracture of lateral lamella of cribriform plate** (MC site of leak)
- **Iatrogenic**: 2nd MC cause; may be following endonasal surgery, FESS, hypophysectomy
- **Spontaneous**: In **idiopathic intracranial HTN** (dura herniates into sella turcica and compresses pituitary and gives it appearance of an empty sella. Dura may herniate thro the defect (**meningocele**) and ultimately brain matter may herniate (**encephalocele**).

Sites and Pathways

- **Anterior cranial fossa CSF**: Reaches nose through the cribriform plate, ethmoid air cells or frontal sinus.
- **Middle cranial fossa CSF**: Reaches nose through the sphenoid sinus
- **Otorhinorrhea**: In transverse temporal bone fracture, CSF enters into middle ear and comes to nasopharynx and nose thro Eustachian tube.

Clinically

- H/O leakage of **clear, watery fluid (sweet taste)** from the nose which **cannot be sniffed back**.
- **Handkerchief test**: NO stiffening of hanky with CSF; whereas nasal discharge will stiffen.
- **Reservoir sign**: Immediately on rising from the bed, patient is asked to place the chin over their chest and stay in that position for one full minute. Clear fluid dripping from the nose is CSF.
- **Double ring/target sign/halo sign**: In traumatic CSF leaks, collect blood from nose on a filter paper or handkerchief; if mixed with CSF blood will stay in center while CSF gravitates to periphery.
- **Paradoxical rhinorrhea** occurs when midline structures that act as separating barriers (e.g. crista galli, vomer) are dislocated. This dislocation allows CSF to flow to the opposite side and manifest at the contralateral nares.

Tests

- **Glucose estimation** (30 mg/dL suggestive of CSF) and **β-trace protein (prostaglandin D synthase)** estimation of CSF are **unreliable tests**.
- On electrophoresis: **β-2 transferrin is specific for CSF, best confirmatory test**.
- Electronic nose: Can differentiate between CSF and serum.
- **CSF tracers** for localization of CSF leak: **intrathecal fluorescein**; **radionuclide cisternography**, **CT cisternography** (Gold standard for localizing **SITE** of leak).
- **High resolution CT** is imaging modality of choice.

Treatment

- **Conservative:** For cases of *immediate-onset CSF rhinorrhea following nonsurgical trauma*. It consists of a **7-10 day trial of bed rest with the patient in a head-up (semisitting) position**, coughing, sneezing, nose blowing, and heavy lifting should be avoided, prophylactic antibiotics to be given; NO nasal packs or drops.
- **Surgical repair** for all persistent cases by **nasal endoscopic** approach.

EPISTAXIS

- MC cause of epistaxis in **children = nose picking**; in **adults = hypertension**.

Septal Anatomy

1. **Little's area/Keisselbach's/locus vasalvae** plexus located in **anteroinferior part of septum** (supplied by both *external and internal carotid arteries*) formed by (**LEGS**):
 - Superior **L**abial artery
 - Anterior **E**thmoid artery (branch of ophthalmic artery which is the **only** branch of the internal carotid artery in this plexus)
 - Septal branch of **G**reater palatine artery.
 - Septal branches of **S**phenopalatine artery. (*artery of epistaxis, since 99% of the nasal mucosa receives its blood supply via this*), **Little' area is MC** site of epistaxis in **children and young adults**. This area gets dried due to effect of inspiratory current and easily injured due to frequent nose picking.
2. **Retrocolumellar vein** runs just behind the columella and crosses the floor of the nose; it is a common source of **venous bleeding in young people**.
3. **Woodruff's plexus**, found in the lateral nasal wall inferior to the posterior end of inferior turbinate. It is anastomosis between the sphenopalatine artery and posterior pharyngeal artery.
4. **Browne's area** is in posterior part of nasal septum; a venous plexus and common cause of posterior epistaxis.

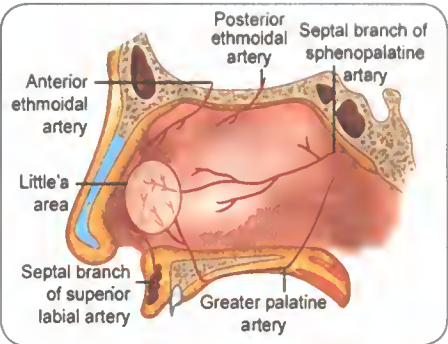


Fig. 18.30: Blood supply of nasal septum

Anterior epistaxis	Posterior epistaxis
Blood comes out of the nose	Blood flows back into pharynx and swallowed
More common	Less common
MC due to trauma	MC due to HTN/arteriosclerosis
MC from Little's area	From posterosuperior part of nasal cavity
Easier to identify	Difficult to identify bleeding point
Mild bleeding	Profuse bleeding
Anterior nasal pack in OPD	Posterior nasal pack in OT under GA

Treatment

- **First aid:** Nasal pinching for 5-10 minutes; Ice at dorsum of nose; In **Trotter's method**, patient is made to sit, leaning a little forward over a basin to spit any blood and breathe quietly from the mouth.
- Cauterization: If bleeding persists cauterize with silver nitrate, electrocautery, endoscopic nasal cautery.
- **Anterior nasal packing**—done in both nasal cavities.
- **Posterior nasal packing** in OT under GA using **Gauze, Foley's catheter or Nasal balloon**.
- Arterial embolization: Of *internal maxillary artery* by neuroradiologist
- Arterial ligation:
 - *External carotid artery* ligation above the origin of superior thyroid artery
 - *Maxillary artery* ligation via Caldwell Luc approach or endoscopic
 - *Ethmoidal artery* ligation in medial wall of orbit.

SEPTAL HEMATOMA

- MC due to **trauma**
- May present with **unilateral or bilateral nasal obstruction**; **smooth rounded swelling** is seen
- Best treatment is **immediate drainage**; or else complications like **septal abscess** (*fever, pain, tenderness on bridge of nose*) and later perforation can occur.

Nasal septal perforation

- Trauma: Nasal surgery, digital (nose picking), physical (repeated cauterization).
- Infections: **Syphilis (Bony part)**—('Phil is Bony!'), TII, Leprosy, Wegener's granulomatosis.
- Neoplasia: SCC, BCC, Malignant melanoma
- Miscellaneous: Chrome gases, cocaine sniffing, idiopathic

DEVIATED NASAL SEPTUM

- Clinically: Nasal obstruction, **Sluder's neuralgia** (high DNS pressing middle turbinates—*anterior ethmoidal N syndrome*), epistaxis.

- **Cottle's test:** A positive cottle test will confirm the fact that narrowing is present in the nasal valve area. This is done by asking the patient to pull the cheek outwards and this maneuver is supposed to open up the area thus reducing the block.
- Treatment: **Septoplasty (conservative septal surgery)**; Submucosa resection of septum; septal surgery can interfere with growth of nasal skeleton and is avoided in children.
- **Crooked nose:** Deviation of **cartilaginous dorsum, bony dorsum and tip** to either side of midline leading to either a C or S-shaped dorsal deformity.

RACTURE OF NOSE

- **Class 1:** Depressed nasal fracture where septum is not involved.
- **Class 2:** Also involves nasal septum.
- **Class 3:** Nasoorbitoethmoid fracture leading to CSF leak and pneumocranium.
- Septal fractures:
 1. **Chevallet #:** **vertical #** septum; results from blow from below.
 2. **Jarjavay #:** **horizontal #** septum; results from blow from front.
- Treatment: Needed only in case of deformity and septal deviation. The **reduction should be done within 2 weeks**, otherwise the fracture heals. **Walsham's forceps** for reducing nasal bones fracture and **Asch's septum forceps** for reducing nasal septal fractures.

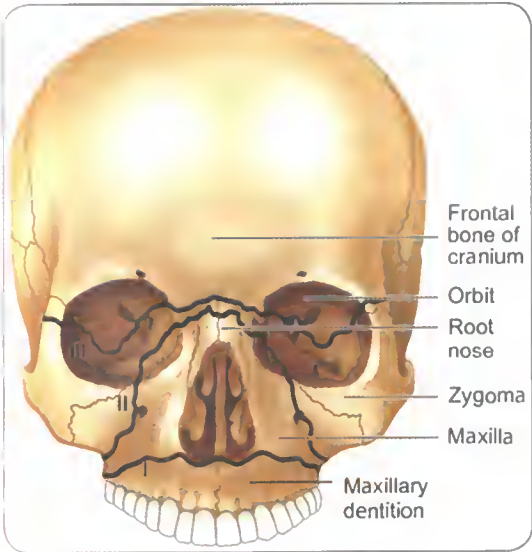


Fig. 18.31: Le Fort classification of fractures of nasomaxillary complex crossing nasal septum and pterygoid plates: (i) Transverse (separating maxillary dentition); (ii) Pyramidal (fracture of root of nose; medial wall and floor of orbit and maxilla), (iii) Craniofacial disjunction (separating face from the cranium)

Fracture of maxilla/Face

- **Le Fort type 1—(Guerin fracture)** Transverse fracture of maxilla involving the palate and floor of nose (separates the maxillary dentition)
- **Le Fort type 2—(Pyramidal fracture)** through **roof of nose and maxilla with damage of infraorbital N**.
- **Le Fort type 3—Complete disruption** of attachment of facial skeleton to the cranium—**craniofacial dysjunction**.

More Important Fracture Points

- **Nasal bone** fracture is **III MC fracture** of body (**I-clavicle; II-wrist**).
- MC site of mandibular # is the **subcondylar region**; **Dingman's** classification is used.
- **Zygomatic #** are called **tripod #** since the bone breaks at 3 places.
- **Blow-out # of orbital floor** shows **tear drop sign** on X-ray/CT scan.
- Extraction of **upper first molar** is **MC cause of oro-antral fistula**.

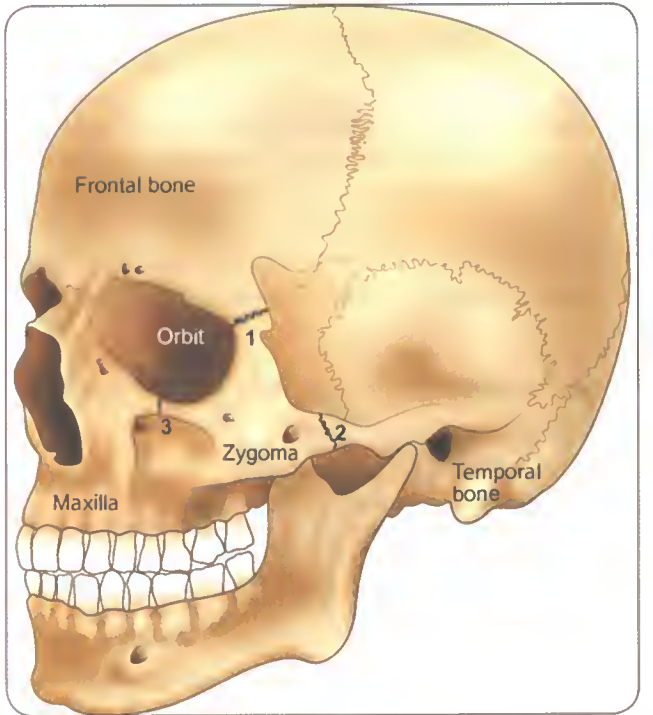


Fig. 18.32: Left zygoma (tripod) fracture showing three sites of fracture. (1) Zygomaticofrontal; (2) Zygomaticotemporal; (3) Infraorbital

INVERTED PAPILLOMA

- Aka **Transitional cell papilloma/Schneiderian papilloma/Ringertz tumour:**

- **MC benign tumor** of nasal cavity.
- It is **pre-malignant lesion**—leads to SCC.
- It arises from **lateral wall of nose**.
- MC in **middle age** and MC in **males**.
- May be a/w HPV.
- Presents with nasal obstruction, rhinorrhea and unilateral **epistaxis**.
- Treatment is **adequate local excision**.

CARCINOMA OF PARANASAL SINUSES

Risk Factors

- For **Squamous cell Ca**: Exposure to industrial fumes, **nickel**-refining processes, and **leather** tanning, exposure to mineral oils, **chromium**, **radium**, **lacquer paint**, **soldering**, and **welding**; **aflatoxin**, **mesothorium** (thorotrast—radiopaque dye); **Bantu tribe** of South Africa.
- For **adeno Ca**: **wood dust**.

Clinically

- **Squamous cell Ca** is MC; **Maxillary sinus Ca** is MC.
- **Nasal obstruction**; **blood stained nasal discharge** and **lacrimation**; dull pain over the face; toothache; in late cases, proptosis and diplopia may occur.
- **Metastases** is rare into the **retroplaryngeal nodes**.
- **Ohngren's line** is a theoretical line that connects the **medial canthus of the eye to the angle of the mandible**; the line divides the maxillary sinus into (1) an anterior-inferior part (tumors that arise here, i.e. **below Ohngren's line**, generally have a **better prognosis**), and (2) a superior-posterior part.

Classifications

- **Ohngren's classification**
- **TNM classification (Lederman's)**
- **AJC (American Joint Committee) classification (followed presently)**.

Treatment

- **Surgery is mainstay** of therapy—Complete **radical maxillectomy** is **main therapy** for maxillary sinus Ca; **Weber ferguson** incision is used.
- **Preoperative and postoperative radiotherapy** may be used.

EXTRA EDGE

- **Frontal sinus Ca** is **rare**;
- **Ethmoidal sinus Ca** is due to **extension of maxillary sinus Ca**;
- **Adenoid cystic Ca**—**perineural invasion** is seen.

NASOPHARYNGEAL CARCINOMA

Etiopathology

- Consumption of **salt cured fish high in nitrosamines**, **cigarette smoking**. **Vitamin C deficient diet**, insence (**polycyclic hydrocarbons**).
- Common in **Southern China, Southeast Asia** uncommon in India except in Northeast India (**mongoloid origin**).
- Arises **MC at fossa of Rosenmuller in lateral wall of nasopharynx**.
- **Squamous cell Ca** is MC
- **WHO classification**: (1) Keratinizing SCC (2) Non keratinizing SCC (differentiated) and (3) Undifferentiated SCC.
- **Epstein-Barr virus (EBV)** is a/w **nonkeratinizing and undifferentiated SCC**.

Clinically

- MC in **males** in 4th–5th decade
- MC presentation is **upper neck swelling** (metastases to **cervical lymph nodes**).
- Unilateral neck swelling is more common than bilateral; lymphatic drainage is to the retropharyngeal nodes (the **earliest LN involved—sentinel node** or **first echelon lymph node**) and jugulodigastric (tonsillar).

Spread of tumor	Features
Nose and orbit	Nasal obstruction, epistaxis
Eustachian tube	Serous or suppurative otitis media leading to unilateral deafness and tinnitus
Parapharyngeal space	Cranial nerve palsies (CN VI MC); Horner's syndrome trismus
Foramen lacerum and ovale	Facial pain and cavernous sinus thrombosis (CN III, IV, V, VI)
Retropharyngeal nodes	Neck pain and stiffness
Krause's nodes	In jugular foramen; enlargement compresses CN IX, X and XI and causes jugular foramen syndrome
Distant metastases	To bone (MC) , lung, liver

Management

- **MRI with gadolinium (contrast) and fat suppression** is the imaging modality of choice.
- **Radiotherapy (RT)** is the **treatment of choice**; **external beam RT** is MC used.

More about Ca nasopharynx

- ▶ In **unilateral serous otitis media in elderly** person, Ca nasopharynx **MUST** be ruled out.
- ▶ **Trotter's triad**: Palatal paralysis (CN X), conductive deafness and ipsilateral pain on side of face/mandibular pain (temporoparietal neuralgia, CN V).
- ▶ In Ca nasopharynx TNM classification, the **node (N) classification is different; less weightage** is given to level 1 and 2 nodes (even 6 cm nodes are N1 category); node enlargement of **supraclavicular fossa or Ho's triangle** (triangle between medial and lateral ends of clavicle and point where neck meets the shoulder) is considered N3.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Etiopathology

- MC benign tumor of nasopharynx (but still quite rare); **slow growing**.
- Common in South East Asia, Middle East and India.
- Occurs commonly in **young adolescent males (almost always)**.
- It is a **highly vascular locally invasive tumor** arising close to the **superior margin of sphenopalatine foramen**.
- Endothelium lined blood channels have **NO muscle coat**, so chance of **bleeding at surgery is more** (MC from **internal maxillary artery**).

Clinically

- **MC initial** symptom is **severe recurrent epistaxis**; **nasal obstruction** is also common.
- Tumor is best seen on posterior rhinoscopy as a **pink/purplish mass**.
- **Denasal** speech (difficulty in saying 'm', 'n' and 'ing' - just like when u have a severe cold!!).
- Others are hyposmia/anosmia; broadened nasal bridge; proptosis and '**frog-face**' deformity; swelling of cheek.
- X-ray of the sinuses: **Bowing of the posterior wall of the maxillary sinus (Antral sign or Holman Miller sign)**.
- **CT scan with contrast** is gold standard; MRI to see soft tissue extension (salt and pepper appearance); Biopsy is **CONTRA**indicated.
- **Hondusa sign**: On X-ray and CT; widening of gap between ramus of mandible and maxillary body on the right side compared to left, suggestive of infratemporal fossa involvement by juvenile angiofibroma.
- **Sessions, Radkowski and Fisch** classifications are used.

Treatment

- Preoperatively to reduce vascularity: **Embolization of feeding vessels**; **estrogen therapy** and **preoperative radiation (not used now)**; **cryotherapy**.

- **Open surgical excision** is **treatment of choice** (endoscopic only for small tumors).
- Radiotherapy for unresectable tumors.
- **Recurrences** are common (up to 50%).

More signs

- ▶ **Stankiewicz's sign**: indicate **orbital injury during FESS**. Fat protrudes into nasal cavity on compression of eye ball from outside.
- ▶ **Tragus sign**: In **acute otitis externa** there is **marked tenderness** when tragus is pressed against the pinna.
- ▶ **Tea Pot sign**: It is **seen in CSF rhinorrhea**. This could be related to the relationship of the sphenoid ostium to the sinus floor. The sphenoid ostium lies at an appreciable distance anterosuperior from the sinus floor. An increase in the CSF rhinorrhea therefore occurs in a case of sphenoid sinus leak when the patient bends forward as an increasing amount of CSF gains access to the ostium.
- ▶ **Dodd's sign/Crescent sign**: X-ray finding-Crescent of air between the mass and posterior pharyngeal wall. **Positive in Antrochoanal polyp**; **Negative in Angiofibroma**.
- ▶ **Uvula pointing sign**—Uvula points to **side of palatal palsy**; seen in rhinoscleroma when scleroma involve nasopharynx, uvula point toward roof of nasopharynx.
- ▶ **Wood's sign**: Palpable jugulodigastric lymph nodes.

TYPES OF OSMIA

- **Anosmia**: **Loss** of sense of smell
- **Cacosmia**: **Perception of bad smell** as in maxillary sinusitis, foreign body in nose etc.
- **Parosmia** is a **distorted/perverted perception of smell** to an odor that is in your environment—for example, a piece of fruit may smell like rotting flesh.
- **Phantosmia (olfactory hallucination)**: Perception of **unpleasant** smell in **absence of any disease process** in the nose or sinuses; may be functional or due to organic lesion, e.g. **temporal lobe epilepsy**, **streptomycin toxicity**, etc.

TYPES OF RHINITIS

- **Rhinitis medicamentosa**: **Iatrogenic** hypertrophic rhinitis due to **prolonged use of decongestive nasal drops (xylometazoline)**.
- **Rhinophyma (potato nose)**: A complication of **acne rosacea** due to **hyperplasia of sebaceous tissue** on the skin of the external nose.
- **Rhinitis sicca**: Ill-defined crusting condition of nasal cavities seen in persons who work in **hot, dry, dusty surroundings**. Excoriation of septal mucosa is often seen.
- **Rhinitis caseosa**: A rare condition in which **cheesy material drains into the nose from the maxillary sinus**.

MORE ONE-LINERS

- **Bleeding polypus of the septum:** A *capillary hemangioma* arising in the anterior part of the septum from Kiesselbach's plexus/L.
- **Giant cell reparative granuloma** is a *benign lesion* due to local reparative reaction, commonly occurring in maxilla. On section the tumor looks like brown tumor of parathyroid.
- In *acute diphtheritic rhinitis*, *epistaxis* is often the main complaint.
- **Cortical olfactory area** is *prepyriform cortex* and *amygdaloid nucleus*.
- In *children unilateral purulent bloodstained nasal discharge* is usually due to *foreign body*.
- **Button/disc battery as foreign body** in the nose should be removed immediately or else *septal perforation and nasal collapse* can occur due to *chemical injury* from *battery leakage*—occurs maximally at the site of contact of *negative pole* of the battery.
- Ammonia which stimulates fibers of the trigeminal nerve is NOT used for testing smell, BUT is used for testing lacrimation (greater petrosal nerve of facial nerve). In nose ammonia stimulates fibers of trigeminal nerve supplying the nasal mucosa. A *patient with complete anosmia* will respond to *inhalation of ammonia*.
- Measurement of *mucociliary flow* is by *indigocarmine test/saccharin test*.
- **Internal nasal valve** is the *narrowest area* of the airway.
- **Nasolabial (Klestadt) cyst:** Smooth bulge in lateral wall of nasal vestibule and obliterates the nasolabial sulcus.
- **BCC (rodent ulcer)** is *MC carcinoma of nose skin*.
- **Mulberry** appearance of nasal mucus membrane is seen in *chronic hypertrophic rhinitis*.
- **Rhabdomyosarcoma** is MC pediatric malignancy of upper respiratory tract.
- **MC site of fibrous dysplasia** is maxilla.
- **MC site of osteoma** in paranasal sinuses is frontal sinus.
- **Olfactory neuroblastoma**, also called *esthesioneuroblastoma* or *esthesioneuroepithelioma* is a malignant neuroendocrine neoplasm that arises from the *olfactory mucosa*.
- **Wegener's granulomatosis:** Necrotizing vasculitis with granulomas of upper and lower respiratory tract, kidneys and skin. Type 1—chronic rhinosinusitis; Type 2—with pulmonary involvement; Type 3—with wide dissemination.
- Parasympathetic or secretomotor fibers to *otic ganglion* are carried by or through the lesser petrosal nerve.

Named nasal conditions

- **Kallman syndrome:** *anosmia* + *congenital hypogonadism* (amenorrhea in females).
- **Samter's triad** consists of *asthma*, *aspirin sensitivity*, and *nasal/ethmoidal polyposis*
- **Kartagener's syndrome:** *Recurrent sinusitis*, *bronchiectasis*, *situs inversus* and *sterility*; due to *dynein defect*.
- **Sluder's (sphenopalatine) neuralgia:** Rhinorrhea, increased lacrimation and nasal stuffiness.
- **Vidian neurectomy** is done in vasomotor rhinitis.
- **NARES:** Non Allergic Rhinitis with Eosinophilia Syndrome.

PHARYNX

PHARYNX ANATOMY

- **Pharynx:** Extends from the base of the skull above to the C6 vertebra below. The pharynx is about **10 cm length** in adult.
 - **Nasopharynx** extends from base of skull up to level of the palatal sphincter and Passavant's ridge at the level of upper border of C2 vertebra.
 - **Oropharynx** extends from the level of palatal sphincter to the level of tip of the epiglottis (C4).
 - **Hypopharynx** (laryngopharynx) extends up to the lower border of cricoid cartilage (C6, lower border). Hypopharynx is divided into **three sub-regions**:
 - *Pyriform sinus* (fossa);
 - *Postcricoid* region and
 - *Posterior pharyngeal wall*.
- **Extrinsic muscles of the pharynx**
 - *Superior, inferior and middle constrictor* (*thyropharyngeus and cricopharyngeus*)—Circular muscle layer.
- **Intrinsic muscles of the pharynx**
 - *Stylopharyngeus, salpingopharyngeus, and palatopharyngeus*—Longitudinal muscle layer.

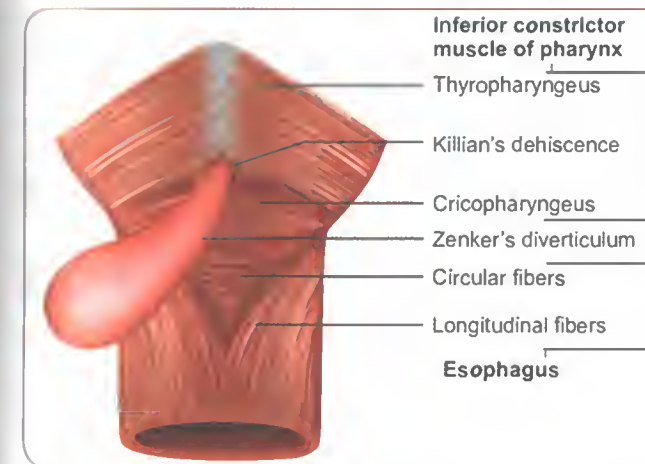


Fig. 18.33: Zenker's diverticulum of hypopharynx herniating through the Killian's dehiscence between the thyropharyngeal and cricopharyngeal parts of the inferior constrictor muscle

Killian's dehiscence

- This is a potential gap between the oblique fibers of the *thyropharyngeus* and the transverse fibers of the *cricopharyngeus*—'Gateway of tears'
- The mucosa of the pharynx may bulge and herniate through this potential space due to muscular weakness resulting in 'pharyngeal diverticulum' or 'pharyngeal pouch'. (Between *thy* and *cryl*).

Waldeyer's Ring

- Aggregated collections of lymphoid tissues are distributed in the pharyngeal mucosa and situated at the junction of the upper respiratory and upper digestive tract in the form of a ring—**Waldeyer's ring**.
- This ring is formed by the *nasopharyngeal tonsil or adenoids (Luschke tonsil)*, *tubal tonsils*, *faucial (palatine tonsils)* and *lingual tonsils*.

Palatine (Faucial) Tonsils

- Tonsils are bilateral ovoid mass of lymphoid tissue on the lateral wall of the pharynx occupying the *interval between the anterior and posterior pillars of the fauces*.
- **Anterior pillar** of tonsil is formed by *palatoglossus* and **posterior pillar** by *palatopharyngeus* muscle.
- Its *medial surface* is lined by *stratified squamous epithelium*.
- There are 10–30 crypts that ramify within the tonsil and may extend as far as its deep surface. In the upper part is the largest crypt—the *intratonsillar cleft (Crypta magna)*.

- The deep surface of the tonsil is bounded by a capsule, which is separated, from the superior constrictor muscle by the *peritonsillar space*.
- Branches of the *glossopharyngeal nerve* lie on the deeper surface of the tonsil. The *internal carotid artery* is 1 inch away from the tonsil.
- **Blood supply** of tonsil—*Tonsillar branch of facial artery* (main supply); others are *ascending pharyngeal artery*; *descending palatine artery*, branch from *lingual artery*.
- *Paratonsillar vein* emerges on the lateral surface and pierces the superior constrictor muscle to end in the *common facial vein*.
- Lymphatics from the tonsil drain into the *jugulodigastric* group of upper deep cervical nodes.

Adenoid Hypertrophy

- **Adenoid facies** (open mouth, flattened midface, long lower third of face, high arching/narrow palate).
- **Reliable objective diagnosis** of **adenoid enlargement** is made by *nasal fiber optic endoscopy*.
- **Adenoidectomy** is typically curative.
- *St Clair Thomson* adenoid curette is used.

TONSILLITIS

Acute Tonsillitis

- **Group A beta-hemolytic Streptococcus** pharyngitis usually occurs in children aged 5–15 years. Viral tonsillitis MC in younger children.
- Clinically:
 - *Fever, sore throat, foul breath, dysphagia* (difficulty swallowing), *odynophagia* (painful swallowing), and tender cervical lymph nodes.
 - Children are most susceptible to infection by those in the carrier state.
- Treatment
 - Antibiotics (penicillin); NSAIDs

Peritonsillar Abscess (PTA, Quinsy)

- It is a collection of pus *between* the *fibrous capsule of the tonsil* (usually at the upper pole) and the *superior constrictor muscle* of the pharynx.
- Patient presents with *severe throat pain, fever, drooling, foul breath, trismus*, and altered voice quality (the '*hot potato*' voice).
- **Anterior pillar** and **soft palate:** *congestion and swelling anterior and superior* to the tonsil; *uvula* is *swollen and pushed to opposite side*; tonsil is enlarged but gets buried behind the anterior pillar.

- Tender cervical adenopathy and torticollis (neck turned in the **cock-robin position**) may be present.
- Ipsilateral otalgia may be observed.
- Treatment
 - Aspiration and incision and drainage (I and D).
 - Interval tonsillectomy: Done after 6 weeks of quiescence.
 - Abscess tonsillectomy/hot tonsillectomy: Performed in acute stage.

TONSILLECTOMY

Indications

Absolute	Relative	As a part of other operations
<ul style="list-style-type: none">• Chronic or recurrent tonsillitis (7 episodes in 1 year OR 5/year for 2 years OR 3/year for 3 years OR 2 weeks or more of lost school or work in a year)• Peritonsillar abscess• Tonsillitis causing febrile convulsions• Cardiac valvular disease a/w recurrent streptococcal tonsillitis• Tonsillar hypertrophy causing upper respiratory obstruction• Suspected malignancy of tonsil	<ul style="list-style-type: none">• Diphtheria carriers who do not respond to antibiotics• Streptococcal carriers• Chronic tonsillitis bad taste or halitosis• Tonsillolithiasis• Difficulty in eating• Failure to thrive	<ul style="list-style-type: none">• Palatopharyngoplasty for Obstructive Sleep Apnea (OSA) syndrome• For pediatric OSA• Glossopharyngeal neurectomy: CN IX is severed in the bed of tonsil• Removal of styloid process

Contraindications

Absolute

- Polio epidemic
- Submucous cleft palate

Others

- Acute tonsillitis
- Age < 3 years
- Recurrent URTI

Types of Tonsillectomy

- **Extracapsular** (total tonsillectomy, subcapsular tonsillectomy).
 - Extracapsular tonsillectomy involves dissecting lateral to the tonsil in the plane between the tonsillar capsule and the pharyngeal musculature, and the tonsil is generally removed as a single unit.
 - The MC extracapsular techniques use a 'cold' knife (sharp dissection), monopolar electrocautery, bipolar cautery (or bipolar scissors), or harmonic scalpel.
 - ONLY extracapsular techniques should be used for patients undergoing tonsillectomy as a result of tonsillitis or peritonsillar abscess.
- **Intracapsular** (partial tonsillectomy, subtotal tonsillectomy—aka tonsillotomy).
 - This involves removal of most of the tonsil, while preserving a rim of lymphoid tissue and tonsillar capsule.

- Preservation of this margin of tissue, this 'biologic dressing,' may promote an easier recovery, with lower hemorrhage rates and better recovery of diet and activity.
- Intracapsular techniques may use the microdebrider, bipolar radiofrequency ablation (which can also be used to remove the entire tonsil), and carbon dioxide laser.
- Either extracapsular or intracapsular tonsillectomy can be performed for the pediatric patient with obstructive sleep apnea.

Important Points about Tonsillectomy

- Position of patient during tonsillectomy: **Rose position**
- **Boyle Davis mouth gag** is used and held in position with **Draffin's lip pads**.
- Method of performing tonsillectomy: **Dissection and snaring** method
- MC cause of bleeding during tonsillectomy: **Paratonsillar vein** (denis Brown vein)

Hemorrhage

- MC complication of tonsillectomy.
- **Primary hemorrhage** wrt tonsillectomy—occurs during the operation; **reactionary hemorrhage**—occurs within 24 hrs of surgery; **secondary hemorrhage**—seen between 5th—10th postoperative day.
- If reactionary or secondary hemorrhage is refractor—take back to OT and reopen and ligate/electrocautery done.

Other complications of adenoidectomy and tonsillectomy

- Nasopharyngeal stenosis
- Atlanto-axial subluxation (**Grisel's syndrome**, RARE)
- Torticollis
- Eustachian tube injury
- Velopharyngeal insufficiency (**hypernasality**, after adenoidectomy)
- Retropharyngeal abscess (after adenoidectomy)



Fig. 18.34: Rose position. The patient lies supine. The head is extended by putting a sandbag beneath the shoulders



Fig. 18.35: Boyle-Davis gag in position

D/D of Membranous Lesions in the Pharynx

- Membranous tonsillitis
- Acute diphtheritic pharyngitis
- Candidal infection
- **Vincent's angina (trench mouth)**: Sloughy ulcer on tonsil and soft palate due to *fusiform bacillus* and *Spirochete denticola*. Dental sepsis is present. Treatment is by antibiotics (penicillin or erythromycin) In addition to analgesics and mouth washes.
- **Infectious mononucleosis**: Caused by EBV; spread by droplet transmission; causes a pharyngotonsillitis with a plaque over the tonsil. Heterophile antibodies are detected by the Monospot test or Paul Bunnell test.
- **Agranulocytosis**.
- **Keratitis pharyngis**: Whitish keratinized outgrowths; unknown etiology; asymptomatic; reassurance needed.

Space	Extent
Retropharyngeal space	Base of skull to tracheal bifurcation (T4)
Parapharyngeal space (lateral pharyngeal or pharyngomaxillary space)	Base of skull to hyoid bone and sub-mandibular gland
Prevertebral space	Base of skull to coccyx

Throat Abscesses

- **Acute retropharyngeal abscess**: Dysphagia, difficulty in breathing, stridor, croupy cough, torticollis, bulge in posterior pharyngeal wall.
- **Parapharyngeal abscess**:
 - Anterior compartment infections: Prolapse of tonsil and tonsillar fossa; trismus; external swelling behind angle of the jaw.
 - Posterior compartment infections: Bulge of pharynx behind posterior pillar; paralysis of CN IX, X XI and XII; swelling of parotid region.

LARYNX

ESSENTIAL ANATOMY OF LARYNX

- Extends from the C3 to lower border of the C6 where it is continuous with the trachea.
- **Cartilages** of larynx: 9 cartilages of which 3 are paired (Arytenoid, Corniculate, Cuneiform) and 3 are unpaired (Thyroid, Cricoid, Epiglottic).
- The **thyroid, cricoid** cartilages and the **basal part of arytenoid** cartilages are made up of **hyaline** cartilage. They may ossify after the age of 25 years.

- The other cartilages of larynx are made of **elastic cartilage** and do NOT ossify.
- **Cricoid cartilage** is a ring of hyaline cartilage located at the inferior aspect of the larynx and is the **only complete ring of cartilage** around the trachea. It is 'signet ring' shaped.
- **Thyroid cartilage** is the **largest** of the laryngeal cartilages.
- **Thyrohyoid membrane** is pierced by **superior laryngeal vessels** and **internal laryngeal nerve**.

- Cricoarytenoid and cricothyroid joints are **synovial joints**.
- **Rima glottidis** is the **narrowest part of larynx** in adults; in children it is the **subglottic region**.
- **Inlet of larynx** is formed by free edge of epiglottis (anteriorly); sides (aryepiglottic folds) and posteriorly (mucus membrane over the interarytenoid fold).
- **Prelaryngeal lymph nodes** in the region of the thyroid isthmus are called **delphic nodes**.
- **Pre-epiglottic space** is the **space of Boyer**

Larynx of Infants is Different

- **Larynx is higher (app. C2-C4)** and **anterior**
- **Funnel shaped** (adult larynx is cylindrical)
- **Tongue is larger**
- **Trachea is shorter**
- **Laryngeal cartilages** are **soft** and collapse easily
- **Epiglottis** is **omega-shaped**
- **Arytenoids** are relatively **large**
- **Thyroid cartilage** is **flat**
- **Submucosal tissues** of infant's larynx are comparatively loose and easily undergo edematous change with trauma or inflammation leading to obstruction.

How can a neonate respire without difficulty while suckling milk?

- Infant's larynx is positioned high in the neck opposite C3 or C4 (vocal cord level) at rest and reaches C1 or C2 during swallowing. This high position allows the epiglottis to meet soft palate and make a nasopharyngeal channel for nasal breathing during suckling. The milk feed passes separately over the dorsum of tongue and the side of epiglottis, thus **allowing breathing and feeding to go on simultaneously**.

Muscles of Larynx

- **Cricothyroid**
 - Only intrinsic muscle lying on **the external aspect of larynx**
 - **Tensor** of larynx
 - Supplied by **external laryngeal nerve** (branch of **superior laryngeal nerve**)
- **Posterior Cricoarytenoid**:
 - Only **ABductor** of vocal cords (**opens** the glottis).
 - Mnemonic: '**P**olice **C**aptured all **AB**ductors!'
- **Lateral cricoarytenoid, transverse arytenoids**:
 - Adductor of vocal cords (**close** the glottis)
- **Thyroarytenoid**

- Upper part = thyroepiglotticus, lower part = vocalis
- All laryngeal muscles are **paired except transverse arytenoid**.
- Regarding vocal cords:
 - **1** muscle **abducts (opens)**; **1** muscle **adjusts the length**
 - **2** muscles **adduct (close)**; **2** muscles **adjust the tension** (Logan Turner's ENT, Pg 144).

Nerve supply of larynx

- **Motor nerve supply**—All the intrinsic muscles of the larynx are supplied by the **Recurrent laryngeal nerve (RLN)**, except the **Cricothyroid** by the **External laryngeal branch of the superior laryngeal nerve (SLN)** (branch of **vagus**).
- **Sensory nerve supply**—**Internal laryngeal nerve** supplies mucus membrane above level of vocal folds. **RLN** supplies it **below** the level of vocal folds.
- The **Galen anastomosis** is a connection between the **RLN** and the **internal branch of the SLN**.
- The '**human communicating nerve**' is an anastomosis between the **external branch of the SLN** and the **distal RLN**.
- Both superior laryngeal nerve and recurrent laryngeal nerve are branches of the **Vagus (CN X)**.

EXAMINATION OF LARYNX

Indirect laryngoscopy	Direct laryngoscopy	Micro-laryngoscopy
Done using a laryngeal mirror . Mirror is warmed before use by placing glass surface on a flame	Done using a rigid laryngoscope ; position is Boyce position or Barking-dog position	This is a combination of laryngoscopy and operating microscopy; started by Kleinsasser

EXTRA EDGE

Blind areas which cannot be visualized on indirect laryngoscopy are:

- Laryngeal surface of epiglottis/infrahyoid epiglottis
- Ventricle of larynx
- Subglottis
- Anterior commissure
- Apex of pyriform fossa

NEUROLOGY OF LARYNX

Nerve Lesions

- **Right Recurrent Laryngeal Nerve (RLN)**: Arises from the **vagus** in the neck and passes **behind the right subclavian A.**
- **Left RLN**: Arises from the **vagus** on the **arch of the aorta** and winds behind it.

- **Unilateral RLN (abductor) paralysis**: Causes the affected cord to lie close to the **midline**; **slight hoarseness** of voice which **improves over days**; **Left RLN palsy** caused by **Pancoast tumor of lung**; **mitral stenosis**; **aneurysm of arch of aorta** and **apical TB**; usually **no treatment required**. **Ortner's syndrome**: paralysis of left RLN in cases of **cardiomegaly**.
- **Bilateral RLN (abductor) paralysis**: The unopposed cricothyroids cause the cords to lie closely apposed. Results in **dyspnea** and **stridor**, especially after exertion; **voice is good**.
- **Combined lesions**: With combined lesions of both the **superior** and **recurrent laryngeal nerves** the cords assume an **intermediate or cadaveric position**.
- However thyroid surgery MC causes combined (complete) paralysis (recurrent and superior laryngeal nerve paralysis).
- '**Bovine Cough**'—A characteristic feature of organic laryngeal paralysis is a **cow-like cough**, which results from the **loss of the explosive phase of normal coughing** consequent upon the failure of the cords to close the glottis.
- **Paralysis of superior laryngeal nerve** causes paralysis of cricothyroid muscle an ipsilateral anesthesia of the larynx above the vocal cord. **Voice is weak and pitch cannot be raised**; may occur due to thyroid surgery, tumors, neuritis or diphtheria.
- MC cause of **vocal cord paralysis** is **iatrogenic (surgical)**.
- **Kashima operation**—**Vocal cord cordotomy**; is done for bilateral **vocal cord paralysis in adduction**. It is considered as an alternative to tracheotomy.

Positions of Vocal Cords

Position of vocal cords	Seen in
Median position (midline)	Phonation and RLN paralysis
Paramedian position (1.5 mm away from the midline)	Strang whisper and RLN paralysis
Intermediate (cadaveric) position (3.5 mm away from the midline)	Both RLN and superior laryngeal nerve paralysis ; this is neutral position of cricoarytenoid joint; abduction and adduction take place from this position
Gentle abduction (7 mm away from the midline)	Quiet respiration and paralysis of adductors
Full abduction (9.5 mm away from the midline)	Deep inspiration

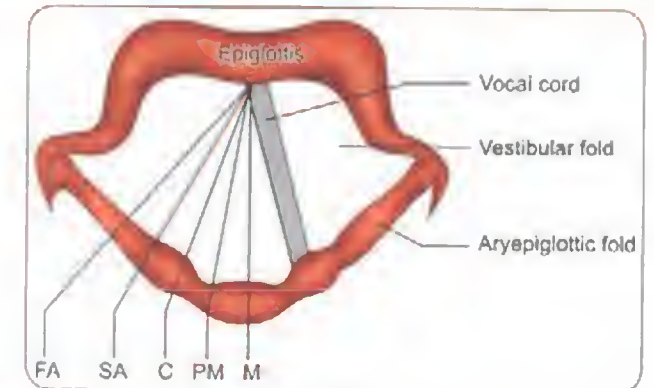


Fig. 18.36: Vocal cord positions

Abbreviations: M = Median; PM = Paramedian; C = Cadaveric (Intermediate); SA = Slight abduction; FA = Full abduction

Laryngeal Surgery

Thyroplasty/Laryngoplasty/Phonosurgery—These are performed to correct incompetent larynx (**glottic incompetence**) caused by **vocal cord paralysis, atrophy or scarring**, and for **voice alteration**. Here the function of the vocal cords can be modified by changing their position and tension, without actually opening the larynx.

The types of thyroplasty introduced by **Isshiki** are given below.

Vocal cord ME dialization (for unilateral vocal cord paralysis)	Type I
Vocal cord LA teralization	Type II
Shortening (relaxing) of vocal cords (anterior commissure set back); lowers the vocal pitch ; Indicated for puberphonia, spasmodic dysphonia	Type III
Lengthening (tightening) of vocal folds (anterior commissure advancement); increases vocal pitch ; male voice converted to female voice —corrects androphonia	Type IV

'**MELA** mein **SA**La!'

CONGENITAL LESIONS OF LARYNX

Laryngomalacia

- MC congenital abnormality of larynx.
- MC cause of **congenital laryngeal stridor/stridor in infants and children**.
- **Excessive flaccidity of supraglottic larynx** which is sucked in during inspiration and child presents with

Inspiratory stridor within 2 weeks of birth; cry is normal.

- Stridor is **relieved** when child is put in **prone** position and **disappears spontaneously** by 2 years of age.
- Direct laryngoscopy: Elongated epiglottis curled on itself (**omega shaped**); floppy aryepiglottic folds and prominent arytenoids.
- A/w **gastroesophageal reflux** disease.

Tracheomalacia

- May be congenital OR a/w **tracheoesophageal fistula** or esophageal atresia.
- A/w expiratory wheeze; honking/**barking** cough; apnea, cyanosis, hypoxia and 'death spells'; supine position makes it worse and prone position relieves it.

Laryngocele

- **Laryngocele** is a dilatation of **laryngeal sacculc**; said to arise from **raised transglottic air pressure**.
- Affects **trumpet** players, **glass blowers** and **weight lifters**.
- May be internal; external (herniates through **thyrohyoid membrane** and presents in the neck) or combined.
- **Bryce's sign** is the gurgling sound produced on pressing the external laryngocele.
- Treatment by **surgical excision**; OR **endoscopic marsupialization** of internal laryngocele.

ACQUIRED LARYNGEAL LESIONS

Vocal Nodules (Singer's Nodes)

- Seen **more in females**, especially **singers, actors, school children** (screamer's nodes) and is caused by **voice misuse**.
- **Bilateral, hard nodules at the junction of the anterior third and middle third** of the free edge of the vocal cords (halfway along the membranous cord).
- **Hoarseness of voice, voice tires easily**, pain in the neck.
- **Non-surgical treatment is often successful**—(**Voice rest, antibiotics and speech therapy**); if unsuccessful, then **microsurgical excision** is undertaken.

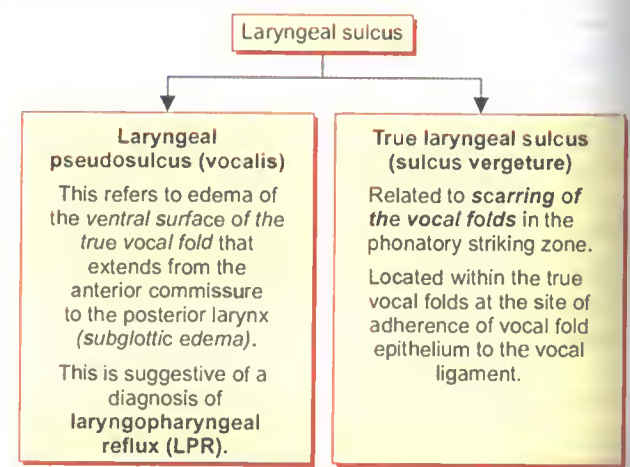
Reinke's Edema

- Results from **smoking** and **voice abuse**; MC in **middle aged women**.
- Bilateral **polypoidal degeneration of vocal cords with swelling along the length of the vocal cords** due to edema of the submucosal space (Reinke's space).
- Treatment is **stripping of the polypoid margin** by **microlaryngoscopy**.

Contact Ulcer

- Due to faulty voice production, vocal processes of **arytenoids rub against each other** which leads to an area of heaped up mucosa on one vocal process which fits into ulcer like depression on the opposite side.
- Risk factors: **Voice abuse, smoking/alcohol**.
- Treatment is to **stop smoking, endoscopic excision of hypertrophic tissue** and **treat gastroesophageal reflux**.

Laryngeal Sulcus



Tuberculosis of Larynx

- Affects **posterior part** more than anterior.
- Almost always **secondary to pulmonary TB**.
- MC affected part is **interarytenoid fold**.
- **Submucosal tubercles** are seen.
- **Pseudooedema** (swollen laryngeal mucosa due to cellular infiltration).
- **Weakness of voice**—earliest symptom.
- **Impairment of adduction**—first sign.
- Laryngoscopy
 - **Mamillated** appearance—Swelling in interarytenoid region
 - **Mouse nibbled** appearance—Ulceration of vocal cord
 - **Turban epiglottitis**—Pseudoedema of epiglottis.

VOICE AND SPEECH DISORDERS

Normal Speech

Speech is an audible communication and consists of **phonation, resonance** and **articulation**.

Expired air pressure and vocal fold vibrations produce **phonation**



Which is modified into voice by **resonance** of the head, neck and chest and motor activity of pharynx and oral cavity



Articulation, which is performed by lips, tongue, palate, pharynx and larynx, shapes the voice into words.

Puberphonia

- **Childhood voice** has **higher pitch**; when the **larynx matures at puberty, vocal cords lengthen** and voice changes to lower pitch in **males**.
- Failure of this change and **persistence of childhood voice** is called **puberphonia** ('Mutational falsetto' and 'Voice break').
- Best treated by voice therapy called **GUTZMAN's pressure test**. Pressure on the thyroid prominence in a backward and downward direction improves the voice.
- **Type III phonosurgery** can be done which includes surgical shortening and relaxation of cord.

Dysphonia Plica Ventricularis

- Here **ventricular folds (false cords)** take over the function of true cords.
- It may be **secondary** to impaired function of true cord (paralysis, tumor) or **psychogenic** (functional).
- Voice is **rough, low-pitched** and **unpleasant**.
- On laryngoscopy—**false cords approximate partially or completely on phonation** and **obscure the view of the true cords**.
- Secondary cases are difficult to treat; functional cases require voice therapy and psychological counseling.

Phonasthenia

- **Fatigue** of phonatory muscles (**thyroarytenoid and interarytenoid**) due to voice abuse resulting in **weakness of voice**.
- Laryngoscopy shows
 - **Elliptical space** between the cords (thyroarytenoid weakness)
 - **Triangular gap** near the posterior commissure (interarytenoid weakness)
 - **Keyhole** appearance of **glottis** (due to both above).
- Treatment: Vocal rest and vocal hygiene.

Rhinolalia

Rhinolalia clausa (Due to nasal/nasopharyngeal obstruction)	Rhinolalia aperta (Due to palatal insufficiency)
Nasal polyp, hypertrophied turbinate, DNS, enlarged adenoids, nasopharyngeal fibroma, rhinitis medicamentosa, choanal atresia	Cleft palate, palatal paralysis, palatal cicatrization, palatal perforation

EXTRA EDGE

Rhinolalia = Nasal intonation and nasal speech

TUMORS OF LARYNX

Divisions of the Larynx

- **The supraglottic larynx** includes the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids.

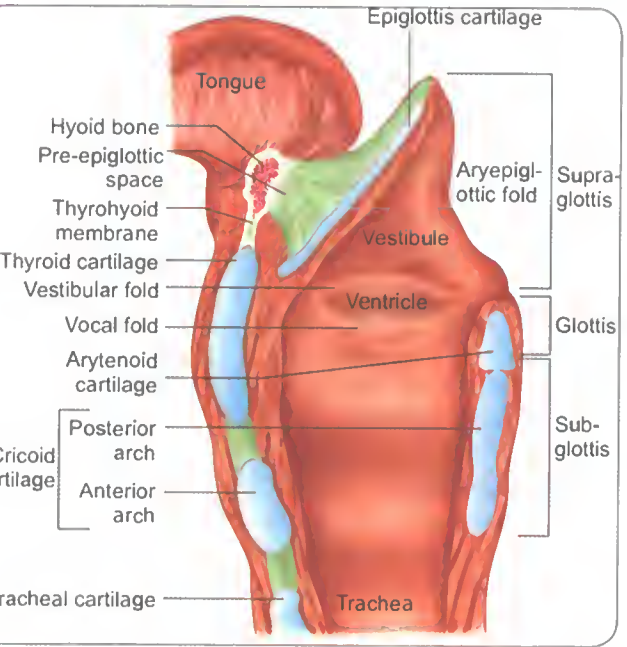


Fig. 18.37: Structures and parts of larynx

- **The glottis** includes the true vocal cords and the anterior and posterior commissures.
- **The subglottic region** begins about 1 cm below the true vocal cords and extends to the lower border of the cricoid cartilage or the first tracheal ring.

Juvenile Onset Recurrent Respiratory

Papillomatosis (JORRP)/Multiple Papillomatosis

- Caused by **HPV 6 and 11** (also 16 and 18); MC in **infants/children**; multiple sessile/pedunculated papillomas that are fireable and **bleed on touch**; MC site is **vocal fold** (other sites are **larynx, nose, pharynx and trachea**); **dyspnea** with **stridor** can occur; **vertical transmission** also occurs.
- Treatment:
- Microendoscopic excision with: **CO₂ laser, cup forceps, cryotherapy, microelectrocautery, microdebrider**. **Recurrence** after removal is common.

- **Other treatments tried:** *Interferon alfa*; methotrexate, indole-3-carbinol (from cabbage and broccoli), intralesional *cidofovir*, 585 nm pulsed dye laser, radiation, vaccines.

Adult Papilloma

- **Smaller** in size; **do not recur** after surgery; MC age affected is **30–50 years**; MC in **males**; **hoarseness** is the presenting symptom; **treatment is same as JORRP**.

Carcinoma Larynx

- **Risk factors:** *Smoking, alcohol, gastroesophageal reflux; asbestos, wood dust, nitrogen mustard, ionizing radiation.*
- Age group = **40–70 years**; MC in **males**
- MC type is **squamous cell Ca**.
- MC type is **glottic cancer**, next is supraglottic and **least common is subglottic**.
- **Glottic cancer:** MC site; **hoarseness** is the MC and early presentation; **best prognosis**; lymph node involvement is late (*since true vocal cords are devoid of lymphatics*); **highly radiosensitive**.
- **Supraglottic cancer:** MC site is **epiglottis**; **pain on swallowing** is first symptom; mass in neck may be first sign; **hoarseness is late**; **prognosis is poor** since patient reports late and **lymph node metastases occurs early to cervical nodes**.
- **Subglottic cancer:** Presents with **stridor**; **worst prognosis**.
- **Verrucous Ca larynx:** a/w HPV 16 and 18; complete **surgical excision** required.
- Highest incidence of distant metastases is seen in **lungs**.
- **Treatment:** For **stage 1 (T1N0M0)** is **radiotherapy**; **stage III** it is **laryngectomy followed by postoperative radiotherapy**.
- **Ashai technique** is a method of **vocal rehabilitation** in patients with laryngectomy.
- **Esophageal speech:** Dynamic component of phonation lies at **pharyngoesophageal segment**.
- **Blom Singer prosthesis:** In laryngectomy patients it is used to divert tracheal air into esophagus for voice production.
- **Laryngofissure** means opening the larynx in the midline.

Laryngeal Cancer Surgery

Type I	Subepithelial cordectomy
Type II	Subligamentous cordectomy

Type III	Transmuscular cordectomy
Type IV	Total/complete cordectomy
Type V	Extended cordectomy

AJCC Staging of Ca Larynx

Primary Tumor (T-tumor)

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma <i>in situ</i> .
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades more than one subsite of supraglottis, with normal vocal fold mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre epiglottic space or medial wall of pyriform sinus.
T4a	Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility .
T1a	Tumor limited to one vocal cord.
T1b	Tumor involves both vocal cords.
T2	Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility.
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage.
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. (As T4b above)
Subglottis	

T1	Tumor limited to the subglottis.
T2	Tumor extends to vocal cord(s) with normal or impaired mobility.
T3	Tumor limited to larynx with vocal cord fixation .
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. (As T4b above)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension.
N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension. Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension. Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension.
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension.
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension.
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension.
N3	Metastasis in a lymph node, > 6 cm in greatest dimension.

Metastases

M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 or T1-3 N1 M0
Stage IVA	T4a N0-1 M0 or T1-4a N2 M0
Stage IVB	T4b N0-3 M0 or T1-4 N3 M0
Stage IVC	T1-4 N0-3 M0

Treatment Algorithm for Ca Larynx

Stage	Treatment
Carcinoma <i>in situ</i>	Endoscopic Excision (stripping/laser)
I and II	External Beam Radiotherapy (EBRT). If EBRT fails, then conservative surgery (cordectomy, partial laryngectomy)
III and IVA without thyroid cartilage invasion	Concurrent Chemoradiotherapy
IVA with thyroid cartilage invasion	Total laryngectomy with adjuvant radiotherapy
IVB and IVC	Palliative radiotherapy

Tracheostomy

- High tracheostomy
 - **Above** the level of the **thyroid isthmus** (isthmus lies against II, III, IV tracheal rings)
 - It violates the first tracheal ring
 - Can cause **perichondritis** of cricoid cartilage and **subglottic stenosis**
 - Always **avoided**
 - **Only** indication—Ca larynx.
- Mid tracheostomy
 - **Preferred** one
 - Through **II or III rings**
- Low Tracheostomy
 - **Below** the level of isthmus

ORAL CAVITY

Conditions a/w malignant transformation in oral cavity

- High-risk lesions**
 - Leukoplakia (**most common**)
 - Erythroplakia (**maximum risk**)
 - Speckled erythroplakia
 - Chronic hyperplastic candidiasis
- Medium-risk lesions**
 - Oral submucous fibrosis
 - Syphilitic glossitis
 - Sideropenic dysphagia: (**Paterson-Kelly** or **Plummer Vinson** syndrome): Achlorhydria, iron deficiency anemia, Esophageal (*hypopharyngeal, postcricoid*) webs, atrophy of mucosa of mouth, pharynx, a/w SCC.
- Low-risk/equivocal-risk lesions**
 - Oral lichen planus
 - Discoid lupus erythematosus
 - Discoid keratosis congenita

Oral Leukoplakia

- Leukoplakia is any white lesion that cannot be removed by simply rubbing the mucosal surface.
- MC premalignant** oral lesion.
- A/w tobacco smoking/chewing; areca nut and betel; alcohol; chronic trauma (ill-fitting dentures); chronic sun exposure; sanguinaria.
- MC in **males**; MC in **buccal mucosa** in Indians.
- Type: homogenous (thin) leukoplakia; nodular (speckled) leukoplakia; erythroleukoplakia.
- Erythroplakia (has 17 times higher malignant potential than leukoplakia)**

Oral Submucous Fibrosis

- Painless oral disease first described by Joshi, in India.** MC in **Asians**.
- A/w prolonged local irritation (**paan masala/supari/areca nut**)
- Pre-malignant lesion.
- Presents with **trismus/restricted mouth opening (MC)**; **ankyloglossia, soreness and burning mouth; vesicles, ulcer and fibrous bands in the mouth.**

Most common

- MC **type** of oral cancer: **Squamous cell Ca**
- MC **site** of oral cancer: **tongue**
- MC **site** of oral cancer in **India: buccal mucosa**
- MC site of **tongue Ca: lateral border**
- MC site of lip Ca: **vermilion of lower lip**
- MRI** is the investigation of choice for cancer of the oral cavity and oropharynx

Oral Candidiasis

- A/w diabetes, immunocompromized, old age, chronic antibiotic use, corticosteroid use.
- Acute pseudomembranous candidiasis (thrush)**: Seen in **infants**; white patch **easily wiped** leaving erythematous base.
- Chronic hyperplastic candidiasis** or **candidial leukoplakia: invasive; premalignant; cannot be easily wiped off**; requires excision.
- Median rhomboid glossitis**: **Red** rhomboid area on **dorsum of tongue**; a/w candidial colonization; asymptomatic.

Ludwig's Angina

- Ludwig's angina** is caused by a virulent **streptococcal** infection a/w anaerobic organisms (*Bacteroides* and *Fusarium*) and sometimes with other lesions of the floor such as carcinoma.

- It is a **cellulitis** of the **submandibular spaces**, often arising from **infection of the mandibular dentition**.
- Clinically:
 - **Brawny (board like)** swelling of the submandibular region combined with inflammatory edema of the mouth; **combined cervical and intraoral signs**.
 - Putrid **halitosis**.
 - The infection encompasses both sides of the mylohyoid muscle causing edema and inflammation such that the tongue may be displaced upwards and backwards, giving rise to **dysphagia**.
 - Unless treated cellulitis may extend below the deep fascial layers of the neck to involve the larynx (deep neck abscess), **causing glottic edema and painful airway compromise**.
- Treatment: **Immediate antibiotic therapy** (cefuroxime with metronidazole); if not responding **drain both submandibular triangles** under local anesthesia.

ODONTOGENIC CYSTS

- Odontogenic cyst are a group of jaw cysts that are formed from tissues involved in odontogenesis (tooth development). Important ones are as following.

Dental Cyst

- Aka **radicular cyst, periapical cyst, periodontal cyst**—are inflammatory cysts which occur as a result of pulp death in the permanent tooth.
- MC cystic lesion of the jaw**, i.e. it is the **MC odontogenic cyst**; MC in **maxilla**.
- Egg shell crackling** may be elicited due to cortical thinning.

Dentigerous Cyst

- Aka **follicular cyst**.
- It envelops the whole or part of the **crown of the uninterrupted permanent tooth**.
- MC site** is **mandibular (lower) 3rd molar tooth**.
- MC type** is **central type**.
- Cyst is lined by **nonkeratinized stratified squamous epithelium** and the fluid inside is **cholesterol rich**.
- Treatment is **enucleation** with removal of the associated tooth.

Odontogenic Keratocyst

- Arise from remnant of **dental lamina**.
- They **grow rapidly, recurrences are common**, can arise anywhere in maxilla or mandible.
- They can be a part of **nevroid basal-cell carcinoma syndrome (NBCCS)** or **Gorlin's syndrome**.

Ameloblastoma (Adamantinoma)

- **Ameloblastoma** is an entirely epithelial **benign tumor** arising from the **dental lamina, Hertwig sheath, epithelial cells of Malassez, the enamel organ, or the lining of dental follicles/dentigerous cysts**.
- Ameloblastoma is the **MC epithelial odontogenic tumor**.
- **MC site** is **posterior mandible** around impacted third molar.
- It causes **expansion of bone**—X-ray shows **soap-bubble or honeycomb** appearance.
- Wide surgical **excision** is needed.

MORE ESSENTIAL POINTS

- Ranula** is a **retention cyst** of **minor salivary glands or sublingual glands** giving rise to a **bluish cystic swelling**

in the **floor** of the mouth. Treatment is by **complete excision**.

- Epulis** means **swelling on the gum**—May be fibrous epulis, giant cell epulis, malignant epulis; **complete excision** is needed.
- Globus hystericus (pharyngeus)**—Patient complains of a lump in the throat. There is no dysphagia. No abnormality is seen on clinical examination or radiology.
- Intubation granuloma** occurs due to traumatic endotracheal intubation and is characterized by a large fleshy granuloma arising from one **arytenoids**; this can be removed endoscopically.
- Openings of the tube of bronchoscope** are known as **vents**.
- Abbe-Estlander flap** is used in the reconstruction of lip, especially in **surgery of lip cancer**.
- Myer cotton staging** is for **subglottic stenosis**.

Pediatrics

NEWBORN

- **Neonatal period:** Birth to under 4 weeks (<28 days).
- **Early neonatal period:** First week of life (<7 days).
- **Late neonatal period:** 7th day to <28th days.
- **Postneonatal period:** Period of infancy from 28th day to <365 days.
- **Perinatal period:** From 22nd week of gestation (>154 days or weighing >500 g at birth) to <7 days of life.
- **Stillbirth:** Fetal death at a gestational age of 22 weeks or more or weighing 500 g at birth.
- **Term neonate:** Neonate born between 37 and <42 weeks (259-293 days) of gestation.
- **Preterm neonate:** Neonate born before 37 weeks (<259 days) irrespective of birth weight.
- **Post-term neonate:** Neonate born at gestational age of 42 weeks or more.

Features of a 'normal' term neonate

- **Length:** 50 cm
- **Head circumference:** 34 cm
- **Chest circumference:** 31 cm (3 cm less)
- **US:LS ratio =** 1.7 to 1.9
- **Heart rate:** 110–160/min
- **RR:** 40–60/min
- **Temperature:** 36.5 to 37.5 °C
- **Attitude:** Flexion
- Peripheral cyanosis (acrocyanosis) may be present.
- Urine is passed by 24 hours after birth.
- **Meconium** (first stool) is passed **within 24 hours**.
- Skull shows molding with parietal bones slightly overriding the occipital and frontal bones.
- There may be pulmonary flow (systolic) murmur, especially in LBW neonates.
- Liver, spleen and kidney may be palpable.

MINOR CLINICAL PROBLEMS IN NEONATE

These occur normally and require NO treatment:

- **Milia:** White dots and face and nose due to distended sebaceous glands; disappear spontaneously.
- **Erythema toxicum:** Erythematous papules on trunk and face; appear on 2nd and 3rd days and disappear spontaneously.

- **Mongolian spots:** Bluish spots, MC in **sacral area** (mainly in lower back and buttock); may also be found in posterior thighs, legs and shoulders; disappear spontaneously before first birthday.
- **Stork bites:** Pink capillary hemangiomas of nape of neck, upper eyelids, forehead and nose; disappear spontaneously.
- **Peeling of skin:** More common in post-term and Intrauterine growth restriction (IUGR) babies.
- **Breast engorgement:** Due to transplacentally acquired maternal hormones; seen on 3rd or 4th days.
- **Epstein pearl:** Epithelial inclusion cysts which appear as whitish spots; may be palatal or prepuceal.
- **Pre-deciduous (natal) teeth:** Supernumerary teeth in central incisors position; they are shed before primary dentition.
- **Vaginal bleeding:** On 3rd to 7th days, due to withdrawal of maternal hormones.
- **Vaginal discharge:** Due to transplacentally acquired maternal estrogen.
- **Hymenal tags:** Around margin of hymen.
- **Physiological phimosis.**
- **Harlequin:** Color change: Division of the body into longitudinal half into **red and pale halves**.
- **Transient neonatal pustular melanosis:** Do NOT contain bacteria or eosinophils; no therapy required.



Fig. 19.1: Mongolian blue spot: The Mongolian spot is found on the sacrum or low back at birth and often disappearing completely within a few years

PRIMITIVE REFLEXES

Reflexes present at birth	Reflexes appearing after birth
<ul style="list-style-type: none"> • Rooting, sucking and swallowing reflex • Crossed extensor reflex • Moro's reflex • Palmar grasp reflex • Asymmetric tonic neck reflex (ATNR) 	<ul style="list-style-type: none"> • Symmetric tonic neck reflex • Parachute reflex • Landau reflex

- A number of primitive reflexes can be elicited in healthy term neonate.
- These disappear as the child grows—these are *inhibited by frontal lobe* as the child grows.
- Persistence of primitive reflexes beyond the typical age suggests abnormal myelination of the higher inhibitory pathways as seen in pre and perinatal **hypoxic ischemic brain injury**.

Reflex	Age of appearance	Age of disappearance
Rooting	34 weeks	4 months (earliest to disappear)
Moro	32 weeks	3–6 months
Palmar grasp	28 weeks	6 months
ATNR	35 weeks	6–7 months

Contd...

DEVELOPMENTAL MILESTONES

Age	Gross motor	Fine motor	Language	Social
1 month	Momentarily lifts head when prone	Has tight grasp, follows objects to midline	Responds to sound of bell	Regards a lighted torch or face of mother intently
2 months	Momentarily lifts head in horizontal plane (in plane of the body); Lifts chest when prone	No longer clenches fist tightly, follows objects past midline	Smiles after being stroked or talked to	Social smile (smile after being talked to)
3 months	Neck/Head holding achieved, i.e. lifts head above horizontal plane	Follows moving objects in a circular fashion, converges and focuses	Coos (musical vowel sounds)	Recognizes parent, reaches for familiar people or objects, anticipates feeding
4 months		Bidextrous reach (reaches for objects with both hands)	Laughs aloud	
5 months	Rolls over , sits with support	Grasps objects/rattle crudely	Orients to voice/bell (localizes laterally)	Enjoys looking around environment
6 months	Sits in tripod fashion (sits with own support); Takes foot to mouth; lifts head and upper chest with support	Unidextrous reach (reaches for objects with one hand); Transfers objects from one hand to another; palmar grasp	Monosyllabic words (ba, pa, da); 'ah-goo' sounds	Recognizes strangers—Stranger anxiety, smiles back at mirror image of self

Contd...

Reflex	Age of appearance	Age of disappearance
Symmetric tonic neck reflex	4–6 months	8–12 months
Landau	10 months	24 months
Parachute	8–9 months	Persists throughout life
Crosses extensor	28 weeks	1–2 months

EXTRA EDGE

- MC cause of depressed or **absent Moro's reflex** is **CNS disturbance**.
- **Asymmetrical Moro's reflex—Erb's palsy** (C5–C6 lesion); spastic hemiplegia; shoulder dislocation; fracture proximal humerus or clavicle.
- **Persistence of Moro's reflex beyond 6 months** is abnormal and indicates **brain damage**.
- **Expanded New Ballard Score** is used to assess gestational age between 20 and 44 weeks.

Domains of Development

Domain	Functions
Gross Motor	Includes milestones related to posture and movement
Fine Motor	Includes manipulation of objects by hand
Language	Includes listening, hearing, understanding and speaking
Personal Social	Includes interaction with self and others

Contd

Contd...

Age	Gross motor	Fine motor	Language	Social
8 months	Sits without support			
9 months	Crawls , cruises, pulls to stand with support	Uses <i>immature pincer grasp</i> , probes with forefinger, holds feeding bottle	Responds to name, says bisyllables mama/dada (non-specific)	Waves bye-bye; Responds to social play, plays pat-a-cake, starts to explore environment (9-10 months); object constancy (understanding the objects continue to exist even when not seen-9 months)
10 months	Pulls from supine to sitting ; from sitting to standing, stands holding furniture		Understands to some extent, e.g. 'where is mama'	
12 months	Creeps well ; walks but falls; stands without support	Pincer grasp mature; gives hand held objects to mother when asked, turns 2-3 pages at a time	Says 'mama, dada' (specific); 2 words with meaning	Comes when called; plays simple ball game
15 months	Walks well without support, walks backwards and sideways	Imitates scribbling, feeds himself with spoon without spilling contents; makes tower of 2 blocks	Uses 3-5 words meaningfully	Temper tantrums, separation anxiety
18 months	Starts to run, climb stairs with help	Makes a tower of 3 cubes, scribbles spontaneously, may draw a vertical line	About 10 words with meaning including name	Copies parents in tasks (e.g. sweeping), toilet training started, ' Domestic mimicry '
2 years	Runs well, climbs stairs alone; walks on tiptoes (30 months)	Makes a tower of 6 cubes, turns one page of a book at a time, copies horizontal line	Points to at least one named body part, simple 2 word sentences made (2 words at 2 years!); uses pronouns ('I', 'me', 'you')	Follows 2-step commands
3 years	Pedals tricycle (3 wheels), stands momentarily on one foot ; jumps with both feet off ground, can alternate feet when climbing stairs; develops handedness (preference to use one hand), can use spoon and cup	Make a tower of 9 cubes, draws (copies) a circle	Uses plurals, 3 word sentences (3 words at 3 years!); Asks questions, knows full name and gender/sex	Dresses and undresses partially buttons/unbuttons
4 years	Hop on one foot; alternates feet going downstairs (At four, u hop off the floor!); catches ball reliably	Draws (copies) a cross and square ; builds bridge with blocks; can identify left and right (left-right discrimination); copies a rectangle (4 and 1/2 years)	Knows colors ; tells story	Buttons clothing fully , plays with other children
5 years	Jumps on one foot, heel to toe walk; skips	Draws (copies) a triangle ; builds gate with blocks	Asks meaning of words	Dresses without supervision

EXTRA EDGE

- **Transitional objects** are used by children between ages '2 and 5 years'. Transitional objects help children make the emotional transition from dependence to independence. They work, in part, because they feel good. They are soft, cuddly, and nice to touch. They are also effective because of their familiarity, e.g. teddy bear, soft toys, blankets etc.
- **Disfluency of speech** (repetition of whole words and phrases) is normal in children between **2 and 4 years** of age. (Stuttering is different which consists of multiple partial word repetitions and irregular, rapid and abrupt repetitions and is associated with distress).

Apgar Score

	0	1	2
Appearance (Color)	Blue or pale	Body pink, extremities blue	Pink
Pulse (Heart rate)	0	< 100	> 100
Grimace to catheter in nose (Reflex stimulation)	No response	Grimace	Cries, coughs or sneezes
Activity (Muscle tone)	Flaccid	Some flexion	Actively moving extremities
Respiratory effort (not rate)	0	Slow irregular	Good crying

- Apgar score is an objective method of evaluating newborn's condition immediately after birth.
- Performed at 1 minute and 5 minutes after birth, BUT resuscitation, must be initiated before the 1 minute score is assigned.
- Thus Apgar score is NOT used to guide the resuscitation-but change of score at sequential times after birth can reflect *how well, the baby is responding to resuscitative efforts*.
- Hence Apgar score should be obtained every 5 minutes for up to 20 minutes if the 5 minute Apgar score is < 7.
- The 1 and 5-minute Apgar scores have almost **NO predictive value** for long-term outcome, and **do NOT predict** neurological outcome.
- **False negative Apgar score** (Acidosis present, BUT Normal Apgar score) is seen in:
 - **Maternal acidosis**
 - **High fetal catecholamine levels**
 - **Some full-term infants.**

GROWTH

Laws of Growth

- The growth follows a **sigmoid** shaped curve.

- The fetus grows fast in the first half of gestation; in the early postnatal period, the velocity of growth is **high in the first few months**.
- Order of growth is **cephalocaudal** and **proximal to distal**.
- The brain enlarges rapidly during the later months fetal life and early postnatal life. By 2 years, it is 75% of adult weight and 90% by 5 years.
- At birth, the head size is about **65-70% of the expected size in adults**. It reaches **90% of adult head size by age of 2 years**.
- Total brain volume at 1 year is 72% and at 2 years is 83% of adult brain volume.
- Maximum growth of **lymphoid tissue** occurs between **4 and 8 years** of age.
- WHO growth charts are based on Multicentre Growth Reference Studies (MGRS) conducted in six countries: USA, Norway, Ghana, Oman, Brazil, and India ('**UNGOBI!!!**').

Bone Age

- To determine skeletal age in infants **between 3 and 9 months**, X-ray of **shoulder** is most helpful.
- A single film of **hands and wrists** is adequate in children between the ages of **1 and 13 years**.
- For children between **12 and 14 years**, X-ray of **elbow and hip** are helpful.

Bone age is delayed (retarded skeletal maturation)

- All cases of **short stature**
- **Constitutional delay** and **undernutrition**
- Systemic illness: **cyanotic congenital heart disease**; rickets; other chronic illness
- Endocrine: **Growth hormone deficiency**; **panhypopituitarism**; **hypothyroidism**, **steroid therapy** and **Cushing's disease**

Advanced bone age (generalized accelerated skeletal maturation)

- Precocious puberty
- **McCune-Albright** syndrome (precocious puberty, polyostotic fibrous dysplasia, café au lait spots), endocrinopathies-acromegaly, adrenal adenomas, etc.
- **Congenital adrenal hyperplasia** (A delayed bone age in congenital adrenal hyperplasia indicates glucocorticoid over-treatment).
- Genetic overgrowth syndromes:
 - **Soto's syndrome** (cerebral gigantism)
 - **Beckwith Wideman** syndrome
 - **Marshall Smith** syndrome

Weight

- **At birth**, the average weight of neonates is about **3 kg**; Indian newborn average weight is 2.8 kg.

- During first few days after birth, the newborn loses extracellular fluid equivalent to about **10%** of the body weight.
- By 10 days of life, **birth weight regained** in most infants.
- First 3 months of life, **subsequently weight gain** at a rate of 25–30 g/day (i.e. **750–900 g/month**).
- Rest of the first year, weight gain is **400 g/month**
- **Remember**, birth weight **doubles** by 5 months (6 kg); **triples** by 12 months (9 kg), **quadruples** by 24 months (12 kg), and is 5 times the birth weight (15 kg) by 3 years.
- On an average, a child gains about 2 kg, every years between the ages of 3 and 7 years, and 3 kg/years till the pubertal growth spurt begins.

Height

- Till **2 years** of age, **length** is measured.
- Birth height is increased **by 50% at 1 year of age; doubles at 4 years** and **triples at 13 years**.
- The average length (height) of a newborn is **50 cm**.
- During **first 6 months**, gain in length is **2.5 cm (1 inch) per month**; from 6 to 12 months, gain in length is 1.25 cm (half inch) per month—hence at **6 months** age, **length = 65 cm** and at **1 year, length = 75 cm**.
- After the age of 4 years, child grows at the rate of **6 cm/year**.
- **Upper segment** = from vertex to symphysis pubis.
- **Lower segment** = symphysis pubis to sole of foot.

Age	US:LS ratio
At birth	1.7:1
1 year	1.6:1
2 years	1.5:1
3 years	1.3:1
5 years	1.2:1
6 years	1.1:1
7 years	1:1
After puberty and in adults	0.9:1

- **Formula** to calculate the US:LS ratio is $\{1.(7-n):1\}$ where n is age in years—example for 5 years is $\{1.(7-5):1\} = 1.2:1$ —which is correct.
- **Increased US:LS ratio:** Rickets, achondroplasia, untreated congenital hypothyroidism.
- **Decreased US:LS ratio:** Spondyloepiphyseal dysplasia, vertebral anomalies.

Head Circumference

- Measured by **crossed tape method** from the **occipital protuberance to the supraorbital ridges**.

- Head circumference increases approximately **2 cm/month for first 3 months**; 1 cm/month between 3 and 6 months, and 0.5 cm/month for 6–12 months.
 - Birth : 35 cm
 - 3 months : 40 cm
 - 3 years : 50 cm
 - 9 years to adult : 55 cm

Macrocephaly

Occipitofrontal circumference greater than 2 SD above the mean for age and sex. Causes are

- **Macrocrania** (Increased skull thickness): Occurs due to: diseases of bone metabolism or hypertrophy of bone marrow resulting from **hemolytic anemia**
- **Hydrocephalus** (Enlargement of ventricles)
- **Megalencephaly** (Enlargement of brain); may be due to following 2 causes:
 - Due to an **embryologic disorder causing abnormal proliferation of brain tissue**: Neurofibromatosis; Tuberous sclerosis; Soto's syndrome; Riley Smith syndrome
 - Due to **accumulation of abnormal metabolic substances**: Alexander disease; Tay Sach's disease; Canavan disease; Mucopolysaccharidoses

Defined as occipitofrontal circumference more than 3 SD below the mean for the given age, sex and gestation.

- Congenital **infections** (Rubella; CMV, Varicella)
- **Syndromic**: Trisomy 18 (Edwards); Trisomy 12; Cri-du-chat syndrome; Angelman syndrome
- **Metabolic**: Fetal alcohol syndrome; Maternal phenylketonuria (PKU).

Craniosynostosis

- The premature fusion of one or more cranial sutures is called craniosynostosis.
- Cranial sutures normally rise during early childhood beginning with the metopic suture (2 months) and last frontal and frontozygomatic sutures (68–72 months).

Craniosynostosis	Premature fusion of
Scaphocephaly (dolicocephaly)	MC type ; sagittal suture
Turriccephaly/Oxicephaly (Turmschädel, tower head or steeple head)	Most severe ; coronal, sphenofrontal and frontoethmoidal sutures
Brachycephaly	Bilateral coronal sutures
Trigonocephaly	Metopic suture
Acrocephaly (tower skull)	Coronal, sagittal and lambdoid (seen in Apert and Crouzon syndrome)

Chest Circumference

- At birth: Chest circumference 3 cm less than head circumference
- At 1 year: Chest circumference = head circumference
- Thereafter: Chest circumference > head circumference

Approximate Anthropometric Values by Age

Age	Weight (kg)	Length/height (cm)	Head circumference (cm)
Birth	3	50	34
6 months	6 (doubles)	65	43
1 yrs	9 (triples)	75	46
2 yrs	12 (quadruples)	90	48
3 yrs	15	95	49
4 yrs	16	100 (doubles)	50

Dentition

- Eruption of **temporary teeth** is **primary dentition** and eruption of **permanent teeth** is **secondary dentition**.
- **Temporary teeth** start erupting at **6 months** of age.
- Temporary teeth start falling at 6 years when permanent teeth start appearing; thus between **6 and 12 years there is mixed dentition**.
- For more about teeth eruptions, see **forensic medicine chapter (Pg 498)**.
- **Delayed dentition** or delayed eruption is considered when there are **no teeth by 13 months of age** (mean + 3 SD).
- Causes of delayed dentition are ('**FRIED** ChoP!'):
 - Familial
 - Rickets
 - Idiopathic, Incontinentia pigmenti
 - Endocrine (Hypothyroidism, hypoparathyroidism, hypopituitarism)
 - Down syndrome
 - Cleidocranial dysplasia
 - Progeria

Instruments used for Assessment of Growth

Parameter	Instrument used
Weight	Weighing machine
Length	Infantometer
Height	Stadiometer
Head circumference	Non-stretchable measuring tape
Skinfold thickness	Harpender's Calipers



Fig. 19.2: Infantometer

SHORT STATURE

Definition: Height below the 3rd percentile or more than 2 SD below the median height (< -2 SD) for age and gender according to the population standard.

If height is < -3 SD, then it is considered **pathological** short stature; however, between -2 to -3 SD considered as physiological short stature.

Causes of Short Stature

Proportionate Short Stature (US:LS Normal)

Normal Variants

- Familial
- Constitutional delay in growth (**MC cause of short stature**)

Prenatal Causes

- Intrauterine growth restriction (placental, infections or teratogen)
- Genetic disorders (chromosomal and metabolic disorders)

Postnatal Causes

- Undernutrition
- Chronic systemic illness
- Psychosocial short stature (emotional deprivation)
- Endocrine causes:
 - Growth hormone insensitivity (Laron's syndrome, primary IGF-1 deficiency)
 - Hypothyroidism
 - Juvenile diabetes mellitus
 - Cushing's syndrome
 - Pseudohypoparathyroidism
 - Precocious/delayed puberty

Disproportionate Short Stature (US:LS Altered)

- **With short limbs:** Achondroplasia, hypochondroplasia, chondrodysplasia punctata, chondroectodermal dysplasia, diastrophic dysplasia, metaphyseal chondrodysplasia, deformities due to osteogenesis imperfecta, refractory rickets; US:LS ratio increased.
- **With short trunk:** Spondyloepiphyseal dysplasia, mucopolysaccharidosis, mucopolysaccharidosis, caries spine, hemivertebrae; US:LS ratio decreased.

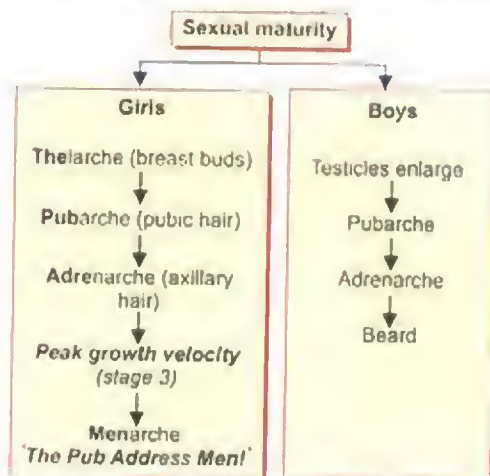
Feature	Constitutional growth delay	Familial short stature
Sex	MC in boys	Both equally affected
Height	Short	Short
Height velocity	Normal	Normal
Family history	Delayed puberty	Short stature
Bone age	Less than chronological age	Normal
Puberty	Delayed	Normal
Final height	Normal	Short, but normal for target height

EXTRA EDGE

- Features of **short stature due to GH deficiency:** US:LS ratio is normal; bone age is less than chronological age by about 2 years; child is normal in height and weight at birth; growth delay is observed after age of 1 year.

Adolescence

- Adolescence is defined as the *period* from the onset of puberty to the termination of physical growth and attainment of final adult height.
- **Adolescent = 10 and 19 years (WHO definition).**
- Early adolescence = 10–13 years
- Mid adolescence = 14–16 years
- Late adolescence = 17–19 years
- **Young people = 10–24 years (WHO definition).**



EXTRA EDGE

- **Peak growth velocity in boys** occurs during later stage of puberty (Tanner's stages 4–5, approximately 13–14 years)
- **Peak growth velocity in girls** occurs during Tanner's **stage 3**
- In **boys** the first visible sign of puberty is **testicular enlargement** (around 9–10 years); testicular volume is assessed using an **orchidometer**
- In **girls**, the first visible sign of puberty is **thelarche** (appearance of breast buds).
- The hormone with a permissive action at the onset of puberty is **Leptin**.
- The primary event at puberty is the **pulsatile release of GnRH**.

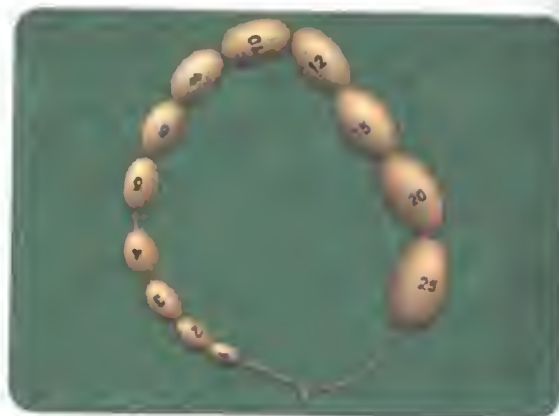


Fig. 19.3: Orchidometer

Breast Growth Stages (as per Tanner)

- **Stage 1:** Prepubertal elevation of **papilla** only
- **Stage 2:** Elevation of breast tissue and papilla as a small mound—**breast bud**
- **Stage 3:** **Enlargement of areola** and breast
- **Stage 4:** Projection of areola and papilla to form a **secondary mound**
- **Stage 5:** Secondary mound disappears. **Adult breast** with typical contour.

NEONATAL DISEASES

Erythroblastosis Fetalis

- **Hemolytic disease of the newborn** (erythroblastosis fetalis) is caused by blood group incompatibility between the mother and fetus.
- **Maternal IgG crosses the placenta** and destroys fetal erythrocytes.
- An **Rh-mother carrying an Rh + fetus** is at highest risk.
- Risk increases when fetal blood crosses into the maternal circulation as in **abortion, ectopic pregnancy, amniocentesis and motor vehicle accidents**.

- Affected neonates present with: **anemia, hyperbilirubinemia, hepatosplenomegaly, pulmonary edema and ascites**.
- The **direct Coombs test** is **positive**.
- Treat with exchange transfusions
- Prevent disease with **anti-Rh IgG injections** for high-risk mothers at 28 weeks of delivery, and at any other time of exposure to fetal blood.

Kleihauer-Betke test

- **Fetal RBCs in the maternal circulation** (**fetomaternal hemorrhage**) can be detected and **quantified** (volume estimated) by this test which exploits the resistance of fetal red cells to acid elution (acid washes out adult Hb out of the mother's red cells, but the fetal RBCs contain HbF which is not washed out).
- This test **should be performed on all Rh (D) -ve women** who deliver a Rh (D) +ve infant.
- The dose of **anti-D immunoglobulin** to be administered to the mother can be estimated by this test.

APT test

- The **Apt test** is **MC used** in cases of vaginal bleeding late during pregnancy (**antepartum hemorrhage**) to determine if the bleeding is from the mother or the fetus.
- A **positive** Apt test: indicates that blood is of **fetal origin**, and could be due to **vasa previa**.
- A **-ve** Apt test: indicates that the blood is of **maternal origin**.
- The Apt test can be used **after birth (postpartum hemorrhage)** if the newborn has **bloody vomiting, bloody stool, or active bleeding from the nasogastric tube**.
- **+ve Apt test:** Indicates that the blood is either due to **GI or pulmonary bleeding from the neonate**.
- **-ve Apt test:** Indicates that the blood is of maternal origin (**swallowed maternal blood** by neonate, either during delivery or during breastfeeding, e.g. from breast fissures).
- Apt test uses **NaOH** (sodium hydroxide)—hence also called 'alkali denaturation test'.

EXTRA EDGE

- Apt test can **also be used to detect the presence of fetal RBCs in the maternal circulation** in cases of suspected fetal-maternal hemorrhage. Since the test is only a **qualitative** determination, the **quantitative Kleihauer-Betke test** is **MC used**.

Hydrops Fetalis

- **Hydrops fetalis** is defined as the **accumulation of extracellular fluid in tissues and serous cavities** in the fetus.
- It is a/w

- **Increased skin thickness (>5 mm); placental enlargement; pericardial effusion; pleural effusion; ascites**
- With complete prevention of Rh problem, **more than 75% of fetal hydrops is due to Nonimmune causes**.

Causes of hydrops fetalis

- **Immune hydrops fetalis** = Mainly due to Rh incompatibility, ABO incompatibility
- **Nonimmune hydrops fetalis** (due to conditions other than Rh incompatibility)
 - **Chromosomal:** Down's, Turner's, triploidy, aneuploidy
 - **Cardiac failure:** Arrhythmias (SVT, heart block), congenital heart disease, AV malformation.
 - **Congenital infection:** TORCHES, Parvovirus B19
 - **Hematological:** Homozygous alpha thalassemia, G-6-PD deficiency
 - **Congenital malformations:** Diaphragmatic hernia, renal abnormality (congenital nephrotic syndrome), lung malformation (adenomatous or lymphangiectasia)
 - **Placental and umbilical cord diseases:** Twin to twin transfusion, chorioangioma, umbilical vein thrombosis
 - **Malignancy:** Neuroblastoma
 - **Others:** Uncontrolled maternal diabetes, severe anemia, thyrotoxicosis, achondroplasia, hypoalbuminemia, hepatitis, meconium peritonitis
 - **Idiopathic** (20%)

Hypothermia

- Newborns are more prone to hypothermia (**axillary temperature < 36.5 °C**) as they have poor heat regulating mechanisms.
- Heat generating mechanisms are:
 - **Peripheral vasoconstriction**
 - **'Nonshivering' thermogenesis in Brown fat** by adrenaline (brown fat is richly vascularized sympathetically innervated fat collection in axilla, groin, nape of neck, interscapular area and periauricular area).
 - **Increased physical activity—crying, increased body movements.**
 - **Universal flexion**
- Clinical features of hypothermia in neonate are:
 - **Peripheral vasoconstriction:** **Acrocyanosis**, cool extremities.
 - **CNS depression:** **Lethargy, bradycardia**, apnea, poor feeding
 - **Increased metabolism:** Hypoglycemia, hypoxia, metabolic acidosis
 - **Tachypnea, respiratory distress, raised pulmonary artery pressure.**

- Prevention of hypothermia: Warm chain-10 steps: (1) warm delivery room, (2) warm resuscitation, (3) immediate drying, (4) skin to skin contact, (5) breastfeeding, (6) bathing postponed, (7) appropriate clothing, (8) mother and baby together, (9) professional alertness, and (10) warm transportation.

Transient Tachypnea of Newborn

- Benign, **self-limiting** condition in **term** neonates.
- May follow **cesarean** delivery without labor or **precipitous** delivery.
- Due to delayed clearance of **lung fluid**.
- Tachypnea present with **minimal/NO respiratory distress**.
- CXR—**hyperaerated** lung fields; **prominent vascular markings**; **prominent interlobar fissure**.
- Oxygen** treatment is adequate with **excellent prognosis** (resolves **within 72 hours**).

Bronchopulmonary Dysplasia

- Aka **chronic lung disease**.
- Etiology: **Prematurity, barotrauma, oxygen toxicity**.
- Abnormal lung mechanics due to structural immaturity, **surfactant deficiency**, **atelectasis**, and **pulmonary edema**.
- In later stages, there is fibrosis and cellular hyperplasia ultimately leading to **respiratory failure**.
- Babies require **prolonged oxygen** therapy or **ventilatory support**.

	Mild supplemental O ₂ for 28 days AND	Moderate supplemental O ₂ for 28 days AND	Severe supplemental O ₂ for 28 days AND
< 32 wks GA at birth	RA at 36 weeks corrected GA or at discharge	< 0.3 FiO ₂ at 36 weeks corrected GA or at discharge	> 0.3 FiO ₂ +/- positive pressure support at 36 weeks corrected GA or at discharge
> 32 wks GA at birth	RA by postnatal day 56 or at discharge	< 0.3 FiO ₂ by postnatal day 56 or at discharge	> 0.3 FiO ₂ +/- positive pressure support at 36 weeks corrected GA or at discharge

Meconium Aspiration Syndrome

- Neonates can aspirate meconium into the lungs and develop meconium aspiration syndrome (MAS).
- MAS is more common in post and **post-term neonates** and small for date babies.

- Consequences of meconium aspiration:
 - Obstructive emphysema or **atelectasis**
 - Chemical **pneumonitis**
 - Surfactant** dysfunction
- Child presents with **respiratory distress within 1 hour of life** that deteriorates within 24–48 hours
- Complications: **Pneumothorax, Pneumopericardium, Pneumomediastinum, Persistent pulmonary hypertension** of newborn.
- CXR**—bilateral heterogeneous opacities, areas of hyperexpansion and atelectasis and air leak.
- Treatment: **Oxygenation, ventilation**.
- Usually improves within 72 hours.
- Latest NRP 2015 guidelines DO NOT advocate tracheal suction even for non-vigorous babies with MAS.

Neonatal Respiratory Distress Syndrome (RDS)

- Aka **hyaline membrane disease**.
- RDS is common in **preterm babies** less than 34 weeks of gestation; MC in **white** preterm infants.
- Overall incidence is 10 to 15% but as high as **80%** in neonates < 28 weeks.
- RDS is due to **surfactant deficiency**; **surfactant production starts at 20 weeks of life** and peaks at 35 weeks.
- Risk factors**: Prematurity; asphyxia, acidosis, maternal diabetes, Cesarean section, multiple gestation.
- Protective factors**: Maternal heroin use; maternal hypertension, prolonged/premature rupture of membranes.
- Pathology: **Collapsed alveoli** alternating with hyperaerated alveoli, vascular congestion and **hyaline membranes** (fibrin rich edema fluid mixed with cytoplasmic and lipid remnants of necrotic epithelial cells).
- Presents with respiratory distress **within first 6 hours of life**.
- Signs**: **Tachypnea, retractions, grunting, cyanosis** and decreased air entry.
- CXR**: **Reticulonodular pattern**; **ground glass** opacity; low lung volume (**low FRC**); **air bronchogram**; **whiteout lungs** (severe cases).
- L:S ratio** = 1:1 (>2 indicates pulmonary maturity normally).
- Surfactant: Albumin ratio = S:A ratio (<35 indicates immature lung; > 55 indicates mature lung).

Treatment

- NICU admission; Avoid hypothermia; Start IV fluids.
- Start **warm humidified oxygen** to keep arterial oxygen between 50 and 70 mmHg (**91–95% SpO₂ saturation**)

since hyperoxia may also contribute to lung injury in pre-terms!

- If SpO₂ cannot be kept at >90% with 40–70% inspired oxygen concentrations, Continuous Positive Airway Pressure (**CPAP**) is given.
- If even on CPAP, SpO₂ is < 90%, assisted ventilation and endobronchial **exogenous surfactant** are indicated—**Insure (Intubate, Surfactant and rapidly Extubated)**.
- Inhaled Nitric Oxide** decreases the need for Extracorporeal Membrane Oxygenation (**ECMO**).

Prevention

- Antenatal corticosteroids** to mothers in preterm labor (< 35 weeks)—**Betamethasone** 12 mg IM, 2 doses 24 hours apart; or **dexamethasone** 6 mg IM every 12 hourly for 4 doses. (total dose is **24 mg** for both).
- (**Betameth better than dexameth** in preventing neonatal death as per latest Nelson's).
- CPAP started at birth** is as effective as surfactant.

Antenatal corticosteroids

- This is given to women at risk of preterm delivery to help in lung maturation.
- Benefits: Reduced incidence of**
 - Respiratory distress syndrome/hyaline membrane disease**
 - Intraventricular hemorrhage**
 - Necrotising enterocolitis**
 - Neonatal mortality (by 40%)**
 - PDA**

Assessment of RDS

- The severity of respiratory distress is assessed by **Silverman-Anderson score (for preterms)** and **Downes score (for any gestational age)**.

Silverman Anderson Score

	0	1	2
Chest movement	Synchr-onized, equal	Lag on inspiration	Seesaw movement
Intercostal retractions	None	Just visible	Marked
Xiphoid retractions	None	Just visible	Marked
Nasal flaring	None	Minimal	Marked
Expiratory grunting	None	Audible with stethoscope only	Audible without stethoscope

Downe's Score

	0	1	2
Respiratory rate	<60	60–80	>80
Cyanosis	None	With < 40% O ₂	With > 40% O ₂
Retractions	None	Mild	Moderate-severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry	Good	Decreased	Absent

Neonatal Sepsis

Early onset neonatal sepsis	Late onset neonatal sepsis
Occurs within 72 hours of life (85% present within 24 hours)	> 72 hours after birth
Is caused by organisms colonising the maternal genitourinary tract; neonate acquires the organisms as it passes through the birth canal	Acquired from the caregiving environment (nursery or ward) and Gram negative bacilli are MC organisms
Group B Streptococci, E coli are the MC organisms (In India, Klebsiella is MC)	Coagulase negative Staphylococci Gram negative bacilli
Pneumonia is more common	Bacteremia and meningitis are more common
Fulminant course with multisystem involvement	Insidious course with focal infections

- Sepsis screen** includes (usually 2 or more markers are considered significant).
 - Total **Leukocyte** count (TLC) of <5000/cu mm or > 20000/cumm
 - Absolute **neutrophil** count of < 1800/cumm
 - I/T ratio** (immature to total polymorphs) of > 0.2
 - Micro ESR** >15 mm in 1st hour
 - Platelet count** of < 150000/cumm
 - CRP** value of >1 mg/L
- Other markers—**procalcitonin, serum amyloid** and cytokines.
- Blood culture** is confirmatory.
- Listeria infection** may produce preterm delivery, intrauterine death.
- Treatment: Start antibiotics as early as possible (ampicillin + gentamicin).

Hypoxic Ischemic Encephalopathy (HIE)

- HIE = Perinatal asphyxia.
- The primary causes of this condition are **systemic hypoxemia and/or reduced cerebral blood flow**.
- Initial response to **hypoxia is increased cerebral blood flow; cerebral edema aggravates HIE**.

- Guidelines from the American Academy of Pediatrics (AAP) for HIE:
 - Profound metabolic or mixed **acidemia** (pH < 7) in an umbilical artery blood sample, if obtained.
 - Persistence of an **Apgar score of 0–3** for longer than 5 minutes.
 - Neonatal neurologic sequelae (e.g. seizures, coma, hypotonia).
 - Multiple organ involvement (e.g. kidney, lungs, liver, heart, intestines).
 - Diffusion weighted MRI is the investigation of choice for neonates with HIE. For preterm infants, ultrasonography is the investigation of choice.
- Treatment:**
 - Adequate ventilation
 - Ensure normal perfusion by saline boluses
 - BP management—mean **BP above 35–40 mm Hg** is necessary to avoid decreased cerebral perfusion
 - Maintain normal blood glucose: **Avoid hypoglycemia and hyperglycemia**
 - **Avoid hyperthermia**
 - Treatment of seizures
 - **Hypothermia therapy** (33–33.5°C for 72 hrs) followed by slow and controlled rewarming for infants with moderate to severe HIE—neuroprotective
- Original Sarnat staging includes EEG + clinical findings
- Modified **Sarnat staging** (clinical findings only) as below:

	Grade I mild	Grade II moderate	Grade III severe
Alertness	Hyperalert	Lethargy	Coma
Muscle tone	Normal or increased	Hypotonic	Flaccid
Seizures	None	Frequent	Uncommon
Pupils	Dilated, reactive	Small, reactive	Variable, fixed
Respiration	Regular	Periodic	Apnea
Duration	< 24 hours	2–14 days	Weeks

Neurological patterns of HIE

Premature newborns

Selective subcortical neuronal necrosis
Periventricular leukomalacia
Focal and multifocal ischemic necrosis
Periventricular hemorrhage or infarction

Term newborns

Selective cortical neuronal necrosis
Status marmoratus of basal ganglia and thalamus
Parasagittal cerebral injury
Focal and multifocal ischemic cerebral necrosis

Neonatal Hypoglycemia

- Hypoglycemia in neonate** is defined as blood sugar < 40 mg/dL.
 - After neonatal period hypoglycemia is defined as < 54 mg/dL.
 - ALSO NOTE: Hyperglycemia in neonate is defined as blood glucose > 125 mg/dL.
- Causes**
- Due to inadequate substrate enzyme function: **prematurity, twins, respiratory distress syndrome.**
 - Due to hyperinsulinism: **Infant of diabetic mother** (large for date), **Erythroblastosis fetalis** (Rh incompatibility), perinatal asphyxia.

Treatment

- Asymptomatic with blood glucose between 20 and 40 mg/dL—direct breastfeeding is started.
- If blood glucose < 20 mg/dL—**Bolus 10% dextrose** 2 mL/kg IV is given; if normoglycemia is not achieved, glucocorticoids are given; if intractable, glucagon, epinephrine or diazoxide may be given.
- ALSO KNOW: Dextrose in concentration > 12.5% is **never used** through peripheral lines as it can cause **thrombophlebitis**.

Clinical features of infant of diabetic mother

Congenital malformations

- Cardiac (VSD, ASD, TGA coarctation of aorta), **VSD is MC**
- Neural tube defect
- Holoprosencephaly
- Sacral agenesis (**caudal regression syndrome**) most specific
- Hydronephrosis
- Renal agenesis
- Duodenal atresia
- Anorectal malformations

General

- **Macrosomia (large for date)**
- Normal head size
- Increased subcutaneous fat
- Birth trauma
- Hairy pinna

Cardiovascular

- Cardiomegaly
- Transient hypertonic cardiomyopathy
- Persistent fetal circulation

Metabolic

- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- **Hyperbilirubinemia**

Others

- Renal vein thrombosis
- Respiratory distress syndrome
- Polycythemia
- **Increased risk of DM in later life**
- **Small (lazy) left colon syndrome**
- Increased incidence of Down syndrome

NEONATAL JAUNDICE

At birth or within 24 hours

Pathologic jaundice (First day jaundice = 'FIRST')

- Fetomaternal blood group incompatibility (Rh, ABO)—**MC cause**
- Intrauterine infection (TORCH)
- RBC enzyme defect (G-6-PD deficiency, pyruvate kinase deficiency, glutathione synthetase deficiency)
- Spherocytosis
- T- α Thalassemia,
- Vitamin K** excess/water soluble Vitamin K
- Metabolic: Oxytocics, hypoglycemia, dehydration; Lucey—Driscoll syn; Crigler-Najjar syndrome.

Between 24 and 72 hours of age

- Physiologic Jaundice**
- Infection: Congenital and acquired
- Polycythemia:** Small for dates, late clamping of cord, fetomaternal and fetofetal transfusion.
- Cephalhematoma** (\uparrow with **ventouse delivery** and hence **neonatal jaundice also**), swallowed maternal blood
- Gut obstruction: Ileus, Hirschsprung's disease

Late onset after 72 hours of age and within first 2 weeks

- Breast milk jaundice**
- Biliary atresia**
- Hypothyroidism**
- Gilbert's syndrome
- Infection: UTI, Herpes, Hepatitis
- Parenteral alimentation in VLBW
- Metabolic diseases** like galactosemia, alpha 1 antitrypsin deficiency, cystic fibrosis, hereditary fructosemia, tyrosinemia.

Essential Points

- Jaundice is a yellowish discoloration of the skin and sclera that indicates an abnormality of bilirubin metabolism or excretion.
- 1 gm of Hb yields 35 mg of bilirubin.**
- The bilirubin can be either **unconjugated (indirect bilirubin—poorly soluble in water)**, or **conjugated to glucuronic acid (direct bilirubin—soluble in water)**.
- Conjugated hyperbilirubinemia** defined as > 30% of total serum bilirubin is **always pathological**.

Inherited Hyperbilirubinemias

	Gilbert syndrome	Crigler-Najjar syndrome	Rotor syndrome	Dubin Johnson syndrome
Inheritance	AD	Type I-AR Type II-AD	AR	AR
Prevalence	3%	Rare	Rare	1:1300 Iranian jews
Serum bilirubin	Unconjugated, mild	Unconjugated, severe	Conjugated	Conjugated

- Visual jaundice in **neonates** indicates that total serum bilirubin (TSB) > 5 mg/dL (in adults TSB > 2 mg/dL only gives rise to visible jaundice!!).
- Level of jaundice correlates with TSB level (as per Kramer's zones):
 - Zone 1: (head and neck)—4–6 mg/dL
 - Zone 2: (chest to umbilicus)—6–8 mg/dL
 - Zone 3: (trunk to knees)—8–12 mg/dL
 - Zone 4: (arms and legs)—12–14 mg/dL
 - Zone 5: (wrists and ankles, palms and soles)—> 15 mg/dL.

Unconjugated (indirect) hyperbilirubinemia

Increased bilirubin production

- Hemolytic anemia
- Disorders of erythropoiesis
- Intestinal hemorrhage resorption (cephalhematoma)

Impaired conjugation

- Physiologic jaundice of newborn
- Breast milk jaundice (**pregnanediol** in breast milk interferes with bilirubin conjugating)
- Hypothyroidism
- Deficiency of **UDP glucuranyl transferase** (e.g. Gilbert disease (mild decrease), Crigler-Najjar syndrome (absent UDPG))
- Hepatocellular disease (e.g. cirrhosis, viral or drug-induced hepatitis)

Conjugated (direct)

Decreased hepatic bilirubin excretion

- Impaired bilirubin transport (e.g. Dubin-Johnson syndrome, Rotor syndrome)
- Hepatocellular disease (e.g. cirrhosis, hepatitis)
- Drug impairment

Extrahepatic biliary obstruction

- Intrahepatic bile duct disease (e.g. primary biliary cirrhosis, primary sclerosing cholangitis)
- Gallstone obstruction of bile ducts (i.e. choledocholithiasis)
- Pancreatic or biliary cancer
- Biliary atresia

Contd...

	Gilbert syndrome	Crigler-Najar syndrome	Rotor syndrome	Dubin Johnson syndrome
Serum bilirubin decrease with phenobarbitol	70%	CJS I-0% CJS II-77%	Not seen	Not seen
UDP glucuronyl transferase activity	Mild decrease	Absent	Normal	Normal
Cholecystogram	Visualized biliary tree	Visualized biliary tree	Gallbladder visualized	Gallbladder NOT visualized
Prognosis	Benign	Mortality due to kernicterus in CJS type I	Benign	Benign
Genetics	UGT1A1 gene	UGT1A1 gene	Unknown	cMOAT/MRP2?ABCC2 gene
Other comments	LFTs and liver histology normal	LFTs and liver histology normal CJS type II—No kernicterus	Delayed BSP (bromsulphthalein) and ICG (indocyanine green) clearance. Increased urine coproporphyrin 1 Liver histology normal	Black liver due to accumulation of dark coarsely granular pigment in centrilobular hepatocytes

Kernicterus

- Irreversible **bilirubin encephalopathy** caused by unconjugated bilirubin (can cross blood brain barrier) toxicity to **basal ganglia**.
- Phase 1: Poor suck, lethargy, hypotonia, altered ensorium
- Phase 2: Fever, hypertonia, progression to opisthotonus
- Phase 3: High pitched cry, convulsions, death.
- Clinically:
 - Extrapyramidal movement disorder (**choreoathetoid** cerebral palsy).
 - **Upward Gaze** limitation.
 - **Auditory** disturbances (**deafness**, failed auditory brainstem evoked response with normal evoked otoacoustic emissions, auditory neuropathy, auditory dyssynchrony).
 - **Dysplasia of the enamel** of the deciduous teeth.
- Toxic effects of unconjugated bilirubin (and thereby chances of kernicterus) are increased by
 - **Hypoproteinemia** (hypoalbuminemia): Since normally unconjugated bilirubin binds to albumin in circulation.
 - Displace bilirubin from its binding site on albumin: drugs (**sulfonamides**), **acidosis**, **increased FFA** (sec to **hypoglycemia**, **starvation** or **hypothermia**)
 - Make neurons more susceptible to toxic effects of unconjugated bilirubin- asphyxia, **hyperosmolarity**, **prematurity**, **infection**.

TREATMENT OF HYPERBILIRUBINEMIA

Drugs/Pharmacological

- **Barbiturates (phenobarbitone):** Induces **UDPG transferase** and enhance conjugation of bilirubin.
- **Metalloporphyrins:** (Tin, Sn and Zinc, Zn)—decrease bilirubin formation by **inhibiting heme oxygenase**.
- **Miscellaneous:** Frequent milk feeding, charcoal and agar—prevent reabsorption of bilirubin from gut.

Phototherapy

- **Most widely used** Rx for unconjugated hyperbilirubinemia.
- It acts by converting unconjugated bilirubin into soluble isomers that can be excreted in urine and feces.
- **Blue-green light (460–490 nm)** is used.
- Mechanisms of phototherapy: **Structural isomerization (main mechanism)**, configurational isomerization, **photooxidation**.
- Effectiveness of phototherapy does NOT depend upon the skin pigmentation of the baby.
- **Administering phototherapy:**
 - Remove all clothes and expose maximal surface area of the body.
 - Light should fall perpendicularly on the body
 - Cover the eyes.
 - Ambient room temperature should be 25–28°C.
 - Monitor **temperature** of baby every 2 to 4 hours.
 - Measure **TSB levels** every 12 hours.

Complications of phototherapy:

- Bronze baby
- Retinal damage
- Loose stool
- Fever
- Purpuric rash with transient prophyrimemia
- Erythematous macular rash.



Fig. 19.4: Phototherapy

Exchange Transfusion

- **Indications for exchange blood transfusion** in infants with Rh-hemolytic disease of the newborn
 - Cord Hb of 10 g/dL or less
 - Cord bilirubin of 5 mg/dL or more
 - Cord blood PCV < 30
- SVET: Single volume exchange transfusion = 80 mL/kg
- DVET: Double volume exchange transfusion = 160 mL/kg

Cut-off TSB Levels for Phototherapy and Exchange Transfusion

Age	Phototherapy Cut-off	Exchange transfusion Cut-off
Term baby, 24–48 hrs	15 mg/dL	20 mg/dL
Term baby, 48–72 hrs	18 mg/dL	25 mg/dL
Term baby, > 72 hrs	20 mg/dL	25 mg/dL
For preterm babies	1% of birth weight in grams	Phototherapy cut-off + 5 mg/dL

Causes of Acute Liver Failure in Neonates

Fetal onset	Perinatal onset
• Neonatal hemochromatosis	• Viral infections (Enterovirus-11, 6, 9, Coxsackie; HSV 1 and 2; HHV

Contd...

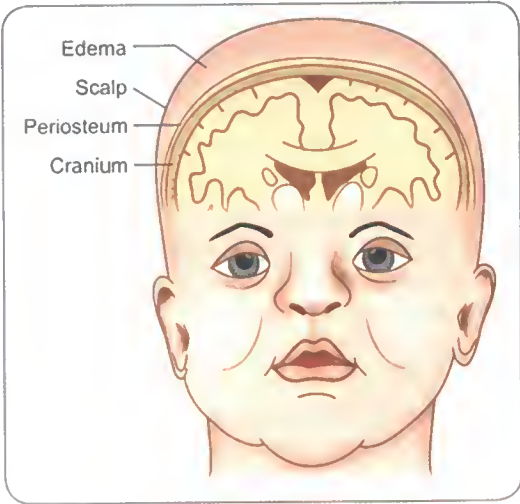
Fetal onset	Perinatal onset
• Hemophagocytic lymphohistiocytosis	• 6; Parvovirus B19, Adenovirus; Paramyxovirus)
• Neonatal lupus	• Inborn metabolic disorders <ul style="list-style-type: none">– Galactosemia– Hereditary fructose intolerance– Hereditary tyrosinemia type 1– Urea cycle disorders
• Neonatal veno-occlusive disease	• Bacterial infections
• Neonatal leukemia	• Drugs
• Inborn errors of bile acid synthesis	• Ischemic (shock liver syndrome)
• Mitochondrial respiratory chain disorders	• Undetermined

Causes of Idiopathic Neonatal Hepatitis (Giant Cell Hepatitis)

- Viral infections
- α 1-antitrypsin deficiency
- Alagille syndrome
- Niemann-Pick type C disease (NPC)
- Progressive familial intrahepatic cholestasis (PFIC)

BIRTH TRAUMA

Caput succedaneum	Cephalhematoma
• Present at birth;	• Seen at 2–4 days old
• May extend over suture lines	• Limited by suture lines
• Mainly edema from venous congestion	• Mainly hematoma
• Diffuse, ecchymotic, edematous overlying skin	• Normal overlying skin
• Disappears spontaneously within 24 hrs after birth	• Reabsorbed over 2 weeks to 3 months; can calcify
• No treatment needed	• May require phototherapy for jaundice



Contd...

Contd

Contd...

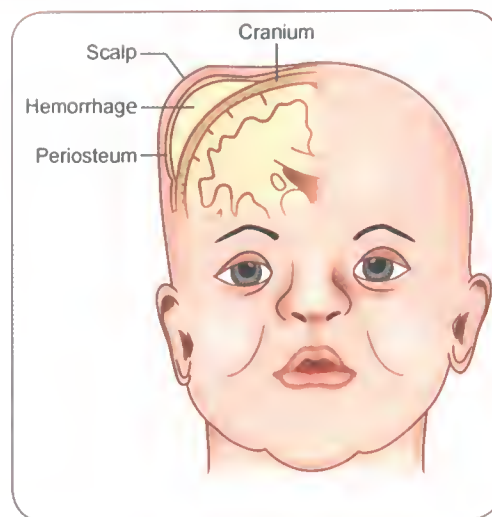


Fig. 19.5: Caput (above) and cephalhematoma (below)

- **# Clavicle:** **MC bone fractured** due to birth trauma; appears at 1–20+ days
- **Sternomastoid** tumor: Appears at 7–20+ days. Intrauterine posture is also a cause. Located at junction of upper and middle third of muscle. **Disappears by 6 months** of age.
- **Brain:** **MC internal organ to be injured** during birth; next MC is liver.

PEDIATRIC CARDIOVASCULAR SYSTEM

Physiology of Fetal Circulation

In the adult, gas exchange occurs in the lungs, BUT in the fetus placenta is the major site of exchange of gases and nutrients.

I. Blood returning to the fetal heart

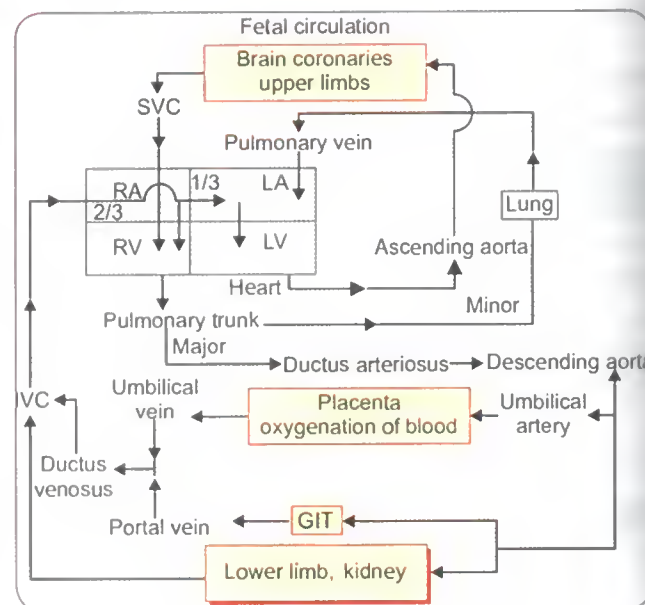
- Blood oxygenated in the placenta returns any way of the umbilical vein, which enters the fetus at the umbilicus and joins the portal vein.
- Most of the umbilical venous blood, shunts through the low resistance ductus venosus to the inferior vena cava (IVC).
- Blood from the IVC (which contains blood returning from hepatic veins, umbilical veins, kidneys and lower extremities) enters the right atrium—here the bloodstream is divided into two by the crista dividens—1/3 of IVC blood enters the left atrium (LA) through the foramen ovale and the 2/3 mixes with the SVC blood (which contains blood returning from head, neck and upper limbs) to enter the right ventricle (RV).

II. Blood leaving the heart

A. Right side: RV pumps out blood into the pulmonary trunk—very small amount of this blood enters the pulmonary circulation since the lungs are collapsed and pulmonary vascular resistance is high. Most of the blood passes through the ductus arteriosus (a shunt between pulmonary trunk and descending aorta) to descending aorta. Descending aorta carries blood to umbilicus through umbilical artery, for oxygenation in the placenta. Descending aorta also supplies blood to lower limbs, kidney and abdominal organs.

B. Left side: The left ventricle pumps blood into the ascending aorta for distribution to coronaries, head and upper extremities. **More important points about fetal circulation**

- The brain and coronary circulation receive blood with higher oxygen saturation (through ascending aorta) than lower half of body.
- The pressure in the right and left ventricles are equal.
- The mean cardiac output is high in fetus—350 mL/kg/min.
- Functional closure of ductus arteriosus occurs within 15 hours after birth.
- In full-term neonates, the ductus arteriosus closes within 10–25 days (anatomic closure).
- Flow through ductus venosus disappears by the 7th day of postnatal life.
- Functional closure of foramen ovale occurs soon after birth, but anatomical closure occurs in about 1 year time.



Congenital Cardiac Disease Associations

Disorder	Cardiac defect	Other features
Holt Oram syndrome	Ostium secundum ASD (MC), 1st degree heart block	Radial ray anomalies
Maternal RUBella	PDA MC; (Rub your Palms During Ascent! since its cold at high altitude!!); VSD, pulmonary artery hypoplasia, pulmonary stenosis.	
Turner's syndrome	Bicuspid aortic valve (MC), COA (2nd MC)	Given separately in Genetics chapter
Infant of diabetic mother	TGV, VSD, COA, PPHN	Given separately below
William's Beuren syn.	Supravalvular aortic stenosis	Elfin facies; mental retardation; hypersocial personality; short stature; hypercalcemia; expressive language disorder
Down's syndrome	MC-ostium primum ASD (aka AV septal defect or endocardial cushion defect), VSD	Given separately in genetics chapter
22q11 syndrome	Truncus arteriosus, TOF	
Noonan's syndrome	Dysplastic pulmonary valve, HOCM	Short stature; dysmorphic facies; webbed neck; developmental delay; cryptorchidism
Fetal alcohol syndrome	VSD, ASD	
Marfan syndrome	MVP, MR, aortic root dilation	Given separately in Ophthalmology chapter
Alagille syndrome	Pulmonary stenosis, TOF	Dysmorphic facies; cholestatic jaundice; butterfly vertebrae, renal anomalies
SLE in mother	Congenital complete heart block	
Ebstein anomaly	Lithium intake in mother during early pregnancy	

Pulmonary Plethora vs Oligemia

Plethora	Oligemia
<ul style="list-style-type: none"> • Pulmonary plethora without cyanosis: left to right shunt like ASD (MC), VSD or PDA • Pulmonary plethora with cyanosis: TGA, TAPVC, Truncus arteriosus, Tricuspid atresia with large VSD 	<ul style="list-style-type: none"> • Tetralogy of fallot (normal sized heart) • Ebstein anomaly (cardiomegaly) and • Tricuspid atresia with pulmonary stenosis

CXR Features of Increased Pulmonary Blood Flow (Pulmonary Plethora)

- Pulmonary: Systemic blood flow ratio more than 2:1 shunt OR left: right shunt of at least 2:1.
- Peripheral pulmonary vessels are visible in **outer third** of the lung (at least **6 vessels** can be traced to outer third).
- Right descending pulmonary arterial (RDPA) diameter > **16 mm** is highly suggestive.
- Ratio of RDPA to trachea > 1.

- Ratio of vessel to adjacent bronchus > 2:1.
- Enface vessels below 10th posterior rib
- Prominent end-on vessels seen at hilum
- Prominent vessels seen below crest of diaphragm.

Axis Deviations

Left ventricular hypertrophy—Left axis deviation	Right ventricular hypertrophy—Right axis deviation
VSD	ASD
Endocardial cushion	TGA
ASD (Ostium primum)	TOF
Truncus arteriosus	Eisenmenger syndrome
Pulmonary atresia	TAPVR
Tricuspid atresia	COA (in infants)
PDA	
COA (in older children)	

NADA's Criteria

The assessment of a child for the presence or absence of heart disease can be done with the NADA's criteria.

Major criteria	Minor criteria	CONGENITAL HEART DISEASE	
<ul style="list-style-type: none"> Systolic murmur grade 3 or more especially with a thrill Diastolic murmur Cyanosis Congestive cardiac failure 	<ul style="list-style-type: none"> Systolic murmur less than grade 3 in intensity Abnormal second heart sound (S2) Abnormal ECG Abnormal X-ray Abnormal blood pressure 	Left to right shunts (Acyanotic)	Right to left shunts (cyanotic)
		<ul style="list-style-type: none"> VSD (MC congenital heart disease) ASD PDA VSD > ASD > PDA 	<ul style="list-style-type: none"> Tetralogy of Fallot (MC cyanotic congenital heart disease) Transposition of great arteries (MC cyanotic lesion in newborn) Truncus arteriosus Tricuspid atresia TAPVR 'STs'

Acyanotic Congenital Heart Disease – Left to Right Shunts

Disease	Anatomy/Symptoms	Signs
Ventricular septal defect (MC Congenital HD)	<ul style="list-style-type: none"> Overall MC congenital heart disease MC congenital heart disease complicated by IE 90% in membranous part of septum Swiss cheese septum—multiple holes in VSD that is difficult to close Small muscular VSDs have the greatest likelihood of spontaneous closure In infants FTT, CCF Gerbode defect = is rare—there is a communication between the left ventricle and right atrium 70-80% VSDs close spontaneously VSD is the MC congenital heart disease to be complicated by IE. 	<ul style="list-style-type: none"> Widely split, variable S2. Pansystolic murmur at left sternal border. Small VSD—Harsher, louder pansystolic (Maladie de Roger)—commonly seen in adults CXR: Biventricular hypertrophy, pulmonary plethora, left atrial enlargement
Patent ductus arteriosus	<ul style="list-style-type: none"> Attachment of PDA just distal to left subclavian artery. In fetus, shunt is right to left (normal), through the ductus arteriosus which connects pulmonary artery and aorta. In first few days of neonatal period, ductus arteriosus should close, if not lung resistance ↓ and shunt becomes left to right with subsequent RVH and failure (abnormal). Risk factors: maternal rubella in 1st trimester, high altitudes. MC in Prematures (recurrent apnea, RDS, CCF); in infants (FTT in addition); in adults (dyspnea, SBE). 	<ul style="list-style-type: none"> Continuous machinery murmur in left infraclavicular area (Gibson's murmur) Mid diastolic flow murmur at mitral valve Differential cyanosis occurs in PDA with reversal of shunt Indomethacin is used to close PDA. ('ENDomethacin ENDs patency of PDA!!') PGE (alprostadil) is used to keep PDA open which is necessary in conditions mentioned below this set of tables.
ASD	<ul style="list-style-type: none"> Ostium secundum (MC), situated in <i>fossa ovalis</i> Ostium primum (AV septal defect, endocardial cushion defect, cleft anterior leaflet of mitral valve) Child: asymptomatic, progressive cyanosis; Adult: breathless from pulmonary HTN Complications: pulmonary HTN, stroke and Eisenmenger's syndrome Syndromes a/w ASD = Holt-Oram syndrome; TAR (thrombocytopenia absent radius syndrome; Down synd; Ellis van Crelld syndrome) 	<ul style="list-style-type: none"> Left parasternal heave (due to RV hypertrophy) Widely fixed split S2 Ejection systolic murmur over pulmonary area Mid diastolic tricuspid flow murmur ECG: rsR pattern with right axis deviation CXR: normal left atrium; small aortic shadow CCF and IE are RARE.

Acyanotic Congenital Heart Disease – Obstructive

Disease	Anatomy/Symptoms	Signs
Aortic stenosis (AS)	<ul style="list-style-type: none"> Infant: valvular (MC) – CCF if severe stenosis Valvular type is MC; Supravalvular: asymptomatic, a/w Williams syndrome 	<ul style="list-style-type: none"> See under valvular heart disease in Medicine chapter

Contd...

Disease	Anatomy/Symptoms	Signs
Coarctation of aorta (COA)	<ul style="list-style-type: none"> Infantile: aortic stenosis proximal to insertion of ductus (preductal) Adult: Postductal, MC coarctation is just below origin of left subclavian A. MC associated cardiac lesion is Bicuspid aortic valve A/w HTN in upper extremities, weak pulses in lower extremities COA is 2nd MC heart disease in Turner syn. 	<ul style="list-style-type: none"> Pulse: radiofemoral delay Elevated upper limb BP Palpable arterial pulsations in interscapular region (Suzzman's sign) Aortic ejection systolic murmur CXR: 3-sign, Dock sign (rib nothing due to collateral circulation)

Cyanotic Congenital Heart Disease

Disease	Anatomy/Symptoms	Signs
Transposition of great arteries (TGA)	<ul style="list-style-type: none"> Cyanosis from birth or shortly after, proportional to shunt through foramen ovale, ductus arteriosus or VSD. Breathless, CCF Most specific heart disease in infant of diabetic mother TGA is a/w uncontrolled PKU in the mother. 	<ul style="list-style-type: none"> Cyanosis persists in 10% oxygen which may even worsen cyanosis by causing closure of ductus Single S2, murmur often absent CXR: Egg on side/string appearance Treatment: Surgery only; Arterial switch operation (distal aorta anastomosed to proximal pulmonary stump (neo-aortic root) and pulmonary artery to proximal aortic stump (neopulmonary artery)).
Tetralogy of Fallot Pulmonary Infundibular stenosis RVH Overriding of aorta VSD ('PROVe!!')	<ul style="list-style-type: none"> Infant: progressively deeper cyanosis, weeks or few months old. Cyanotic (Hypoxemic spells, 'Tet spells,') spells from infundibular spasm—hallmarks of severe ToF; MC start at age 4–6 months—it is characterized by (1) sudden onset of cyanosis or deepening of cyanosis; (2) dyspnea; (3) alterations in consciousness, from irritability to syncope; and (4) decrease or disappearance of the systolic murmur (as RV outflow tract flow becomes completely obstructed). Childhood: squatting after exertion to overcome dyspnea. Squatting cause compression of femoral arteries ↑ pressure, thereby ↓ the right to left shunt and directing more blood from the RV to the lungs 	<ul style="list-style-type: none"> Central cyanosis, clubbing, right ventricular heave. Single S2. Ejection systolic murmur at third left interspace. CXR: cour en sabot (boot shaped heart due to RVH) BUT normal sized heart; pulmonary oligemia; right aortic arch (25% patients) ECG: Right axis deviation, inverted T wave, P pulmonale CHF does NOT commonly occur in ToF
Eisenmenger's syndrome	<ul style="list-style-type: none"> Uncorrected VSD, ASD, PDA → ↑ pulmonary vascular resistance due to arteriolar thickening → progressive pulmonary hypertension. As pulmonary resistance ↑ the shunt reverses from L → R to R → L shunt which causes late cyanosis (clubbing and polycythemia) Most dangerous cardiac lesion in pregnancy 	<ul style="list-style-type: none"> Loud P2

Cyanotic Congenital Heart Disease – Obstructive

Pulmonary Valve Stenosis	<ul style="list-style-type: none"> No symptoms in mild or moderate stenosis. Cyanosis and a high incidence of right-sided HF in ductal-dependent lesions. 	<ul style="list-style-type: none"> RV lift with systolic ejection click heard at the third left intercostal space. S2 widely split with soft to inaudible P2; grade I–VI/VI systolic ejection murmur, maximal at the pulmonary area. Dilated pulmonary artery on chest radiograph
---------------------------------	--	---

Common Mixing Congenital Heart Disease: Acyanotic and Cyanotic

Disease	Anatomy/ Symptoms	Signs
Truncus arteriosus	• Neonate: breathless, CCF	• Minimal cyanosis, Bounding pulse, Single S2, short systolic murmur
Total anomalous pulmonary venous connection (TAPV)	• Newborn: obstructed venous return simulates RDS. Onset 2 months to 2 years. Breathless, FTT • Supracardiac type is MC	• Cyanosis NOT improved in 100% oxygen. Poor pulse. Loud S2. Murmur often absent mild cyanosis, tachypnea, right ventricular heave • CXR: Pulmonary edema with Snowman heart (figure of 8 heart or 'cottage leaf')

Key: CCF = Congestive cardiac failure; CHD = Congenital heart disease; FTT = Failure to thrive; IE = Infective endocarditis; LVH = Left ventricular hypertrophy; PS = Pulmonary stenosis; RDS = Respiratory distress syndrome; RVH = Right ventricular hypertrophy; SBE = Subacute bacterial endocarditis.

More about Tetralogy of Fallot (TOF)

Complications of TOF	Management of anoxic spells in TOF
<ul style="list-style-type: none"> Erythracytosis/polycythemia Brain abscess, Infective endocarditis, Neurological: cerebrovascular thrombosis, hemiplegia, paradoxical embolism to CNS Acute gouty arthritis, delayed puberty Anemia reduces the exercise tolerance, and can result in cardiac enlargement and CCF making the diagnosis difficult 	<ul style="list-style-type: none"> Knee chest position (squatting) Humidified oxygen Morphine Propranolol Correct acidosis with IV sodium bicarbonate Vasopressors (methoxamine) IM or IV drip Correct anemia Palliative Operations

EXTRA EDGE

- Pentalogy** of Fallot = Tetralogy of Fallot + ASD (or patent foramen ovale).
- Trilogy** of Fallot = ASD + RVH + PS (pulmonary stenosis)
- D/D of **breath holding** spells = **seizures; cardiac arrhythmias, brainstem malformations.**
- Iron deficiency anemia can worsen breath holding spells

Treatment of Tetralogy of Fallot

- It was common in the **past** to do temporary (**palliative**) surgery during infancy for TOF. This surgery improved blood flow to the lungs. A complete repair of the four defects was done later in childhood.
- Now, TOF usually is fully repaired in infancy. **However**, some babies are too weak or too small to have the full repair. They must have temporary surgery first. This surgery improves oxygen levels in the blood. The surgery also gives the baby time to grow and get strong enough for the full repair.
- Palliative operations:**
 - Blalock-Taussig** shunt: Subclavian artery to pulmonary artery.
 - Pott's** shunt: Descending aorta to pulmonary artery
 - Watersan's** shunt: Ascending aorta to pulmonary artery
- Complete intracardiac repair**
Widening of the pulmonary stenosis and replacement of pulmonary valve is done; repair of the VSD is done.



Fig. 19.6: X-ray chest of a one-year-old child shows a boot-shaped heart produced by elevated left ventricle combined with a small or absent main pulmonary artery segment and vascularity of the pulmonary artery is reduced



Fig. 19.7: TGA. Note the cardiomegaly, RV apex, RAE, narrow base and marked increase in lung vascularity. The 'egg on side' appearance with lung oligemia can be seen



Fig. 19.8: TAPVC unobstructed and supracardiac. Classical 'figure of 8' appearance can be seen

Additional Points about Congenital Heart Disease

- In adults: ASD is the MC** congenital heart disease VSD is second MC.
- Patent Ductus Arteriosus (PDA) (ductus dependant blood flow) is beneficial** (i.e. if closure is avoided) in:
 - Hypoplastic left heart
 - Pulmonary stenosis
 - Eisenmenger's physiology
 - TGA with intact ventricular septum
 - Interrupted aortic arch.
- Endocardial fibroelastosis:** In infants with critical aortic stenosis, the left ventricular shortening fraction is usually decreased and the endocardium may be bright on ECHO, indicating the development of endocardial fibrous scarring known as endocardial fibroelastosis.
- Norwood procedure**—is performed for **hypoplastic left heart syndrome**.
- Shone complex:** **Coarctation of aorta + mitral valve abnormalities** (supravalvular mitral ring or parachute mitral valve) + subaortic stenosis – this group of **left sided obstructive lesions** occurring together is called Shone complex.
- Ross procedure**, replaces a patient's **damaged aortic valve with his or her own pulmonary valve (autograft)**; the **pulmonary valve is in turn replaced by a human donor valve (homograft)**.
- Katz Wachtel Phenomenon:** Common ventricular hypertrophy in moderate VSD is a/w equiphasic QRS complex esin all precordial leads.

CHF in Children

- MC cause of CHF in infants: congenital heart disease.

- MC cause of CHF in older children: rheumatic fever and RHD.
- Causes of CHF in neonates:**
 - Non-cardiac disorders** (MC cause in first 24 hours): Sepsis, severe anemia, metabolic causes acidosis, hypothermia, hypoglycemia, hypocalcemia.
 - Cardiac causes:** Duct dependent systemic circulation (hypoplastic left heart syndrome, critical AS, severe coarctation, arch interruption); TAPVR (obstructed); congenital MR, TR; neonatal Elstein anomaly
- Clinical features of CHF in infants is given in below table.
- Treatment: **ACE inhibitors** (drug of choice); diuretics; beta blockers.

Left-sided failure	Failure of either side	Right-sided failure
Tachypnea	Cardiac enlargement	Hepatomegaly
Tachycardia	Gallop rhythm (S3)	Facial edema
Cough	Peripheral cyanosis	Jugular venous engorgement
Wheezing	Small volume pulse	Pedal edema
rales in chest	Lack of weight gain	Ascites (in older children)
Hoarse cry	Low urine output (oliguria)	
Pulmonary edema		

RHEUMATIC FEVER

Etiology

- Rheumatic fever is a consequence of **pharyngeal infection** with **group A β-hemolytic streptococcus**. ('*Rheumatic fever from Pharyngitis!*').
- Immune mediated **type 2 hypersensitivity**, not direct effect of bacteria.

Duckett Jones Criteria for the Diagnosis of Rheumatic Fever (1992)

Major criteria

- Carditis (occurs in 90% patients; it is **pancarditis**; **mitral valve** MC involved and **MR** is MC disease; **Carey Coomb's** murmur may be heard due to MR—soft, low pitched mid diastolic murmur). Carditis is the MC major criteria of RF in children whereas in adults with RF, it is arthritis.
- Polyarthritis (**migratory** polyarthritis, **NO** residual joint damage; dramatic response to salicylates)
- Chorea (St. Vitus dance; estrogen or pregnancy can cause recurrences; can occur in isolation)
- Erythema marginatum (**face is spared**)
- Subcutaneous nodules (**nontender** and along **extensor** surfaces; often a/w carditis)

Minor criteria
Clinical
➤ Fever
➤ Arthralgia
➤ Previous rheumatic fever, rheumatic heart disease
Laboratory
➤ Acute phase reactants: Raised ESR, CRP or leukocytosis
➤ Prolonged PR interval on ECG

Essential criteria
➤ Supporting evidence of preceding streptococcal infection within past 45 days: recent scarlet fever, raised antistreptolysin O titer (ASLO), or other streptococcal antibody, positive throat culture or rapid antigen test for streptococcus

2015 American Heart Association (AHA) Revision of Jones Criteria

- The last revision of the original Jones criteria was done in 1992 when ECHO was not so widely practiced; However, in **2015**, the AHA revised the Jones criteria.
- The salient difference between the older criteria, is the **inclusion of echocardiography for diagnosis of subclinical carditis**. In case of **rheumatic mitral valve prolapse**, it may be noted that **only the leaflet tip will bend into the left atrium**, unlike the body of the valve leaflet in classical mitral valve prolapse.
- Another important highlight is **inclusion of monoarthritis and polyarthralgia** as potential major criteria in populations with moderate to high risk of rheumatic fever.
- **Low grade fever** has also been included in the **minor** criteria in such populations.
- For diagnosis of **recurrence of rheumatic activity**, even **three minor criteria**, without any major criteria can also be considered.

2015 Revised Jones Criteria

A. For all patient populations with evidence of preceding GAS infection	
Diagnosis: Initial ARF	2 major manifestations or 1 major plus 2 minor manifestations
Diagnosis: Recurrent ARF	2 major or 1 major and 2 minor or 3 minor
B. Major criteria	
Low-risk populations*	Moderate- and high-risk population

Carditis	Carditis†
▪ Clinical and/or subclinical (subclinical carditis indicates echocardiographic valvulitis) Arthritis	▪ Clinical and/or subclinical Arthritis
▪ Polyarthritis only	▪ Monoarthritis or polyarthriti
Chorea (St. Vitus dance)	▪ Polyarthralgia†
Erythema marginatum	Chorea
Subcutaneous nodules	Erythema marginatum
	Subcutaneous nodules

C. Minor criteria	
Low-risk populations*	Moderate- and high-risk populations
Polyarthralgia	Monoarthralgia
Fever (≥38.5°C)	Fever (≥38°C)
ESR ≥60 mm in the first hour	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL [‡]
and/or CRP ≥3.0 mg/dL	
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

EXTRA EDGE

- Key to above table: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; and GAS, group A streptococcal infection; ARF, Acute rheumatic fever.
- **Low-risk** populations: Those with **ARF incidence ≤2 per 100,000** school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.
- Moderate to high risk: Children not clearly from a low-risk population.
- The inclusion of **polyarthralgia** as a major manifestation is applicable only for moderate- or high-incidence populations and only after careful consideration and exclusion of other causes of arthralgia, such as autoimmune, viral, or reactive arthropathies; joint manifestations can only be considered in either the major or minor categories but not both in the same patient.
- Regarding Echocardiography in the 2015 Jones criteria
 - **Echocardiography with Doppler** should be performed in all cases of confirmed and suspected ARF.
 - It is reasonable to consider performing **serial echocardiography/Doppler** studies in any patient with diagnosed or suspected ARF even if documented carditis is not present on diagnosis.
 - Echocardiography/Doppler testing should be performed to assess whether carditis is present in the absence of auscultatory findings, particularly in moderate- to high-risk populations and when ARF is considered likely.

Prevention of ARF
Primary prevention of ARF:
➤ Treatment: When antibiotic therapy is provided within 9 days of pharyngitis , acute rheumatic fever can be prevented.
➤ Drug of choice is single IM injection of benzathine penicillin G ; erythromycin is DOC in penicillin allergic patients .
➤ Suppressive therapy —For 12 weeks— aspirin (used if no carditis) and corticosteroids (used if carditis present or carditis + CCF present).
Secondary prevention of ARF:
➤ Single IM injection of Benzathine penicillin 1.2 Million units once every 3 weeks.
➤ Patients without proven carditis should receive prophylaxis for 5 years after last episode, or until age of 18 years (whichever is longer).
➤ Patients with carditis (MR or healed carditis) should receive prophylaxis for 10 years after last episode or until 25 years of age (whichever is longer).

Respiratory Sounds

Sound	Cause	Character
Snoring	Oropharyngeal obstruction	Inspiratory, low pitched irregular
Grunting	Partial closure of glottis	Expiratory; occurs in hyaline membrane disease
Rattling	Secretions in trachea or bronchi	Inspiratory, coarse; can be felt by placing hands over the chest
Stridor	Obstruction larynx or trachea (above thoracic inlet)	Inspiratory, may be a/w an expiratory component
Wheeze	Lower airway obstruction (below thoracic inlet)	Continuous musical sound; predominantly expiratory in nature

EXTRA EDGE

- **Grunting** is MC heard in diseases with **decreased FRC** (pneumonia, pulmonary edema) and **peripheral airway obstruction** (bronchiectasis).

Respiratory Infections

	infectious Croup (laryngotracheobronchitis)	Acute epiglottitis (emergency)
Etiology	MC parainfluenza virus1 ; others—RSV; parainfluenza types 2, 3; influenza virus1 adenovirus	MC by streptococci (<i>H influenzae</i> b rare now due to wide prevalence of hib vaccination)
Presenting age	3 months to 3 years	3–7 years

Typical Localizing Signs for Lung Pathology

Type of pathology	Respiratory rate	Chest retractions	Audible sounds
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extra-pulmonary	↑	↑↑	Wheezing
Intrathoracic intra-pulmonary	↑↑	↑↑	Wheezing
Alveolar interstitial	↑↑↑	↑↑↑	Grunting

Congenital Lung Lesions

- **Congenital lung cysts:** Formed by abnormal detachment of a segment of primitive foregut.
- **Bronchogenic cysts:** More common, complications are infection, abscess formation, and rupture into bronchi/pleural cavity.

Bronchopulmonary Sequestrations

The presence of **lobes or segments of lung tissue without** a normal connection to the airway system and with **blood supply derived from the aorta** or its branches, Not the pulmonary artery.

Intraobar sequestration	Extraobar sequestrations
▪ Found within lung parenchyma	▪ Found more often in infants and children as abnormal mediastinal masses in alliance with other congenital anomalies
▪ Common in adults	
▪ A/w recurrent infections	

Congenital Lobar Emphysema

- **Neonatal respiratory distress** with hyperinflation and **enlargement of one lobe** of lung and **mediastinal shift** to opposite side.
- MC affects **left upper lobe**; MC in **boys**; may be a/w **congenital heart disease**.
- **Treatment:** Lobectomy of affected lobe.

Contd...

	Infectious Croup (laryngotracheobronchitis)	Acute epiglottitis (emergency)
Clinically	Prodrome with URI symptoms for 1–7 days; low grade fever, inspiratory stridor that worsens with agitation; hoarseness of voice, barking/metallic/brassy cough ; Westley score is used for grading severity	Rapid onset (4–12 hours) ; high fever, dysphagia, drooling, muffled voice, stridor ; patients may be in 'sniffing' position with neck hyperextended and chin protruding
X-ray	'Steeple sign' on AP view neck film	'Thumb sign' on lateral neck film; absence of well defined vallecula – 'vallecula sign'
Treatment	Racemic epinephrine nebulization —for moderate to severe croup; indications are stridor at rest; possible need for intubation; respiratory distress and hypoxia. <ul style="list-style-type: none">• Single dose dexamethasone—0.6 mg/kg-oral or IM• Cool Mist therapy• Oxygen or heliox therapy	<ul style="list-style-type: none">• Hospitalise patient; start O₂ therapy• IV antibiotics (3rd generation cephalosporin)• If worsening endotracheal intubation or tracheostomy• No sedation



Fig. 19.9: Steeple sign



Fig. 19.10: Plain X-ray soft tissue neck – lateral view showing 'thumb' sign (acute epiglottitis)

Pneumonia

- Few pediatric aspects are discussed below; all other aspects are in the respiratory system chapter (Pg 805).
- **MC** cause of **pneumonia** in **children-viral-RSV**
- **MC bacterial** cause of pneumonia: **Streptococcus pneumoniae** (**pneumococcus**).
- **Tachypnea** is a more specific and more reproducible sign of pneumonia in children than auscultatory signs!

Classification of Pneumonia in a Child (WHO Revised 2014)

- Applicable to **child aged 2–59 months** with cough and difficult breathing.
- Severe pneumonia includes the previous classifications **'very severe pneumonia'** also.

• NOTE: oral **amoxicillin** is the first drug of choice.

Category	Severe pneumonia	Pneumonia	NO pneumonia
Signs and symptoms	Fast breathing and/or chest indrawing PLUS danger signs (stopped feeding, stridor, convulsions, vomiting, lethargic or unconscious, central cyanosis or severe malnutrition)	Fast breathing and/or chest indrawing Respiratory rate cut-offs are as follows: <ul style="list-style-type: none">• > 60/min in 0–2 months• > 50/min in 2–12 months• > 40/min in 12–60 months	ONLY cough and cold

Contd...

Contd...

Category	Severe pneumonia	Pneumonia	NO pneumonia
Treatment	GIVE first dose oral amoxicillin and refer immediately for parenteral antibiotics (ampicillin/penicillin should be used as first line)	Oral amoxicillin 40 mg/kg/dose twice daily (80 mg/kg/day) for 5 days	Home care advice

Bronchiolitis

- **Bronchiolitis** is caused by **Respiratory syncytial virus** (**RSV** also causes **pneumonia**).
- **1–6 months** old infants **affected**; **MC** in **boys**.
- Bronchiolar mucosal inflammation, **edema, thickening, formation of mucus plugs** and **cellular debris**.
- No URI followed by tachypnea, wheezing and respiratory distress. Fine crepitations and rhonchi may be heard.
- CXR- hyperinflation and infiltrates; Leukocytosis.
- Generally self limiting in 3–7 days; asthma may develop in 25% cases
- Treatment: NO antibiotics; symptomatic Rx (oxygen); **Ribavirin** shortens the course of bronchiolitis in children with congenital heart disease, chronic lung disease or immunodeficiency.
- **Palivizumab** is a humanized monoclonal antibody against RSV; administered as monthly IM injection for prophylaxis in high-risk patients.

Bronchiolitis Obliterans

- Bronchiolitis obliterans is characterized by fixed **airway obstruction**; inflammation and scarring occur in the bronchioles, resulting in severe shortness of breath and dry cough.
- **FEV1 reduced** to 20%.
- Symptoms include: dry cough; shortness of breath; wheezing.
- CXR-**hyperinflation**.
- **Associations:** **rheumatoid arthritis**; inflammatory bowel disease; post lung or Bone marrow transplant; penicillamine induced; **Sweyer james** Macleod syndrome (unilateral hypertranslucent lung).
- Severe cases may require lung transplantation.

Cystic Fibrosis

- **Cystic fibrosis** is the **MC life limiting autosomal recessive disease** in Caucasians

- Due to mutation in gene encoding the chloride conductance channel-CFTR gene on **chromosome 7q**; MC mutation is **delta 508**.
- Clinical presentation:
 - Neonates: Meconium ileus
 - Early childhood: recurrent bronchiolitis in infancy
 - Recurrent LRTI, chronic lung disease, bronchiectasis, steatorrhea
 - Adults-pancreatitis, pancreatic insufficiency and azoospermia
- **MC** infecting organism is **non-mucoid** strains of **Pseudomonas aeruginosa**.
- Diagnosis:
 - **Increased sweat chloride** (> 60 mEq/L) on at least **two occasions**
 - Nasal epithelium potential difference testing
 - Detection of **fecal elastase** levels.

EXTRA EDGE

- False positive sweat testing (causes of increased sweat chloride)**
- **Metabolic:** Glucose-6-phosphate deficiency, adrenal insufficiency, nephrogenic diabetes insipidus, mucopolysaccharidoses, fucidosis, panhypopituitarism, pseudohypoaldosteronism, hypothyroidism
 - **Insufficient sweat:** Ectodermal dysplasia, Riley-Day syndrome, malnutrition, dehydration
- False negative sweat test:**
- Edema, hypoproteinemia

Pulmonary Alveolar Proteinosis

- This disorder is characterized by the **intraalveolar accumulation of pulmonary surfactant**.
- It is due to **deficiency of protein B** component of surfactant, which results in impaired spread and absorption of major phospholipid of surfactant.
- Thus there is functional deficiency of surfactant and failure of expansion of alveoli.
- Usually newborn is full term and may have **positive family history**.
- Child usually present with **respiratory distress immediately after birth** which **does not respond to surfactant**.
- There may be **ground glass** appearance on CXR.
- Histopathological examination of lung biopsy specimen is the gold standard for diagnosis—distal air spaces are filled with a granular, eosinophilic material that stains positively with periodic acid-Schiff reagent and is diastase resistant.

Classification of Asthma according to Severity

	Symptoms	Night-time symptoms	PEFR
Intermittent	<1 time a week; asymptomatic and normal PEFR between attacks	≤2 times a month	>80% predicted; variability <20%
Mild persistent asthma	> 1 time a week but < 1 time a day	>2 times a month	≥ 80% predicted; variability 20–30%
Moderate persistent asthma	Daily use of b-2 agonist; attacks affect activity	>1 time/week	>60%, <80% predicted; variability >30%
Severe persistent asthma	Continual symptoms; limited physical activity	Frequent	≤60% predicted; variability >30%

PEDIATRIC GASTROINTESTINAL CONDITIONS

Congenital Diaphragmatic Hernia

(P)Oster(L)ateral hernia Bochdalek's Hernia (POLAR Bear!)	Morgagni Hernia (retrosternal anterior hernia)
<ul style="list-style-type: none">Due to persistence of the pleuroperitoneal canal.MC diaphragmatic hernia in children, MC on left side.Classic triad of respiratory distress, apparent dextrocardia and a scaphoid abdomen; apex beat is shifted to right	<ul style="list-style-type: none">Defect is between the sternal and costal attachments of the diaphragm.Usually occurs on Right side, in adults, particularly females.MC involved viscus is the transverse colonBetter prognosis

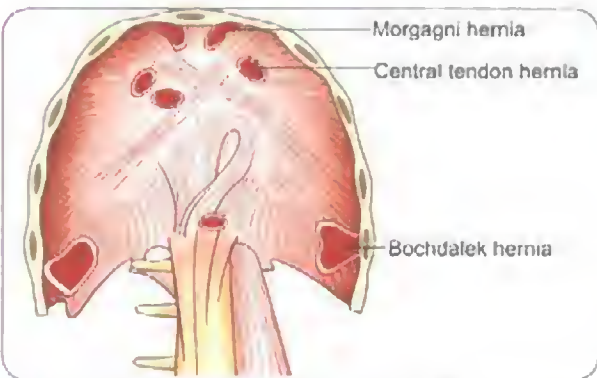
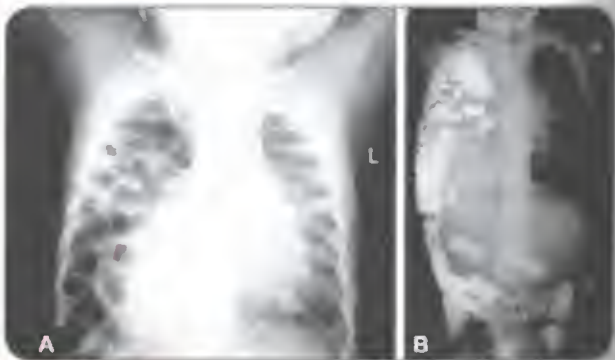


Fig. 19.11: Anatomy of diaphragm showing different sites where hernia can occur

- Pulmonary hypoplasia** is the **MC** cause of death hence, medical therapy is directed toward **optimizing oxygenation** while **avoiding barotrauma**.
- In the delivery room, if the infant is known or suspected to have **congenital diaphragmatic hernia** immediately place a vented **orogastric tube** and **connect it to continuous suction** to prevent bowel distension and further lung compression.
- For the same reason, **avoid bag and mask ventilation** (or give **very minimally**) and **immediately intubate the trachea**.
- Sudden deterioration during resuscitation may be due to **tension pneumothorax**.
- Surgical repair** after stabilization is the **treatment of choice**.

Poor Prognostic Factors

- Polyhydramnios
- Intrathoracic liver and stomach
- Early postnatal presentation (i.e. presenting in 18 hours vs. after 24 hours)
- Coexistence of cardiac CNS or other anomalies
- Persistently elevated pCO₂ or decreased pO₂
- LHR < 1.4 mm (lung to head ratio).



Figs 19.12A and B: A. Plain X-ray chest; B. Barium enema, showing bowel loops within thoracic cavity on the right side (diaphragmatic hernia)

EXTRA EDGE

- Eventration of diaphragm:** Abnormally elevated position of one or both hemidiaphragms from **paralysis or atrophy of muscle fibres**.
- Traumatic hernia:** Blunt injury of diaphragm may cause diaphragmatic rupture more often on **left side**.

Esophageal Atresia and Tracheo-esophageal Fistula

- Affects **1 in 4500**; **MC** in **males**.
- MC** type is **esophageal atresia with lower pouch communicating (fistula) with the trachea**-corresponds to type C in Gross classification and type 3b in Vogt classification system.

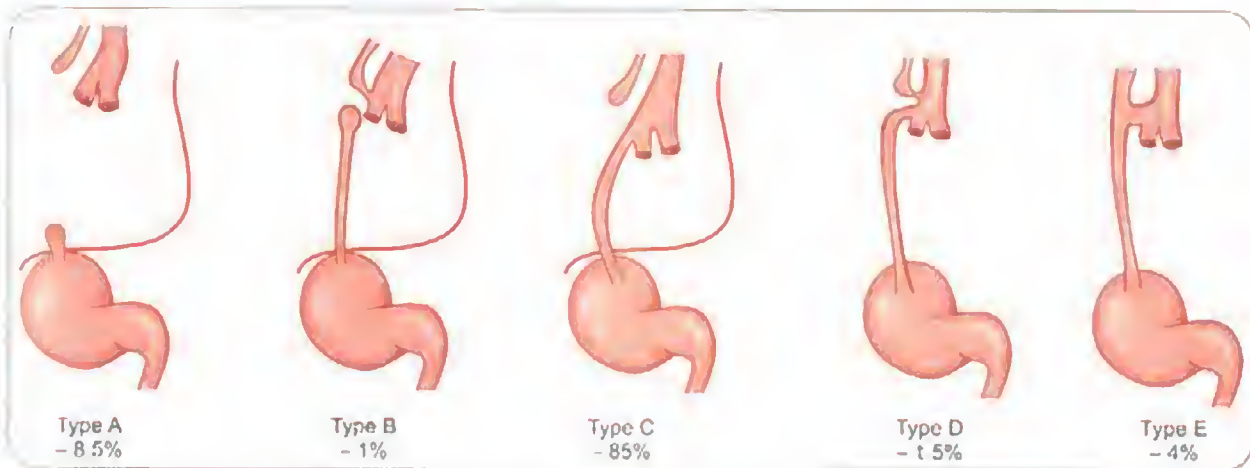


Fig. 19.13: Gross classification of TOF - Type A: Atresia without fistula - 8.5%. Type B: Atresia with proximal TOF - 1%. Type C: Atresia with distal TOF - 85% (commonest). Type D: Atresia with both proximal and distal TOF - 1.5%. Type E: No atresia but 'H' type TOF - 4%

- Affected infants present in **first few hours of life** with **drooling of saliva continuously** and **cyanotic episodes** on attempting to feed; **regurgitation of first feeds** occurs.
- Associations: Maternal h/o **polyhydramnios**; **VACTERL**—Vertebral defects imperforate Anus, Cardiac defect (PDA/VSD), **T**ra-cheoEsophageal fistula, **R**adial and **R**enal dysplasia, **L**imb buds.
- Complications:** Respiratory distress, aspiration pneumonia, gastric distension from air.
- Avoid contrast radiology; use **endoscopy** instead.
- Gasless abdomen** is typically present in **type B**.
- Except for VLBW babies and those with major congenital heart disease, most infants with repaired esophageal atresia have a **good prognosis**.
- Immediate **surgical correction** is required—right sided thoracotomy and repair.
- Feeding gastrostomy is often required.
- Spitz classification is a prognostic classification (group I has best prognosis).

- Palpable 'olive'** shaped mass in epigastrium (pathognomonic)
- Constipation
- Hypochloremic, hypokalemic metabolic alkalosis** (with **paradoxic aciduria**).
- Ultrasound** is the **investigation of choice**; findings are:
 - Doughnut sign**
 - Pyloric muscle 4 mm** or more in thickness
 - Pyloric canal length > 14 mm**
 - Cervix sign** on long axis; **target sign** on short axis.
- Treatment:
 - Correction of dehydration and metabolic abnormalities followed by **Ramstedt's pyloromyotomy** (mucosa is left intact).
 - Atropine** is tried as medical treatment to relax the pylorus



Fig. 19.14: Visible gastric peristalsis

Infantile Hypertrophic Pyloric Stenosis

- Hypertrophy of circular muscle** of pylorus leading to gastric outlet obstruction.
- Affects **first born male infants** at **2 weeks** of life (range 1–8 weeks).
- Increased risk if infant gets **erythromycin/azithromycin** in first 14 days after birth
- Clinical features:
 - Nonbillious projectile vomiting**
 - Visible gastric peristalsis (VGP)**

Duodenal Atresia

- Affects **1 in 10,000** livebirths.
- it is **MC type of intestinal atresia**; it is usually a **complete stenosis of II part** of duodenum at the level of ampulla of Vater.
- Type I:** Complete duodenal atresia is **MC**—may be a/w 'windsock deformity' (an incomplete diaphragm exists with central aperture).
- Associations: **Down's syndrome**; **annular pancreas**; incomplete rotation of gut; anorectal malformations; maternal **polyhydramnios**.
- Plain X-ray abdomen: 'Double bubble' sign with absence of air in the distal part.
- Treatment: **Duodenoduodenostomy** with **Kimura's diamond** shaped anastomosis.

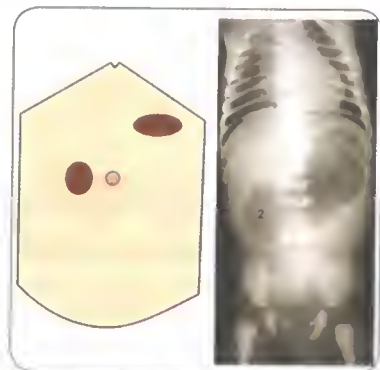


Fig. 19.15: Double-bubble sign in duodenal atresia

Hirschsprung's Disease

- Absence of ganglion cells/enteric nerve plexuses** (Auerbach's and Meissner's) in colon on rectal biopsy.

Stage		Systemic signs	Intestinal signs	X-ray signs	Treatment
Stage I: Suspected NEC	IA	Temperature instability, Apnea, Lethargy	Elevated pre-average residuals; mild abdominal distension; occult blood in stool	Normal or mild ileus	Nil Per Orally (NPO); IV antibiotics X 3 days
	IB	Same as IA	Same as IA + gross blood in stool	Same as IA	Same as IA
Stage II: Definite NEC	IIA (Mild)	Same as I	Same as I + absent bowel sounds; abdominal tenderness	Ileus, Pneumatosis intestinalis	NPO; IV antibiotics for 7–10 days
	IIB (Moderate)	Same as I + mild metabolic acidosis and thrombocytopenia	Same as I + absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, right lower quadrant mass	Portal vein gas shadows	NPO; IV antibiotics for 14 days
Stage III: Advanced NEC	IIIA (Intact bowel)	Same as IIB + hypotension, bradycardia, respiratory acidosis, metabolic acidosis, DIC, neutropenia	Same as II + signs of generalized peritonitis, marked tenderness and distension of abdomen	Same as IIB + definite ascites	NPO; IV antibiotics for 14 days; fluid resuscitation, inotropic support; mechanical ventilation; paracentesis
	IIIB (Bowel perforated!)	Same as IIIA	Same as IIIA	Same as IIB + pneumoperitoneum	Same as IIIA + surgery (resection of infarcted bowel)

- Narrowing of aganglionic segment with dilation of proximal normal colon; can be a **short (75%)** or long segment.
- Presents at infancy or within first 2 years of life.
- Failure to pass meconium**, abdominal distension, chronic constipation.
- Staged procedure** with initial diverting colostomy and later resection when infant > 6 months old.
- If there is **failure to pass meconium** within 48 hours next step will be lower GI study (barium enema).
- On inserting finger into the anus, 'toothpaste like' stools may be passed.
- Associations: Down's syndrome; RET proto-oncogene on chromosome 10 (rarely 13).
- Definitive **diagnosis** is by **full thickness rectal biopsy**.
- Definitive operation: 'pull through' operation (Duhamel's; Swenson's; Soave's).
- Hirschsprung's disease is aka **congenital megacolon**.

Necrotising Enterocolitis

- Necrotising enterocolitis (NEC)** is an **acquired inflammatory condition of neonatal gut (intestinal necrosis)** occurring primarily in watershed distributions; it is not congenital; affects children **0–2 months of age**.
- Pathogenesis:** Prematurity; formula feeds; bacterial infection; impaired gut blood flow; cong. heart disease.
- Signs:** (See following table)
- Treatment:** (See following table). Breast milk protects against NEC.
- Modified Bell's staging system of NECs are as follows:**

Intussusception

- Telescoping of a bowel segment into itself may → edema, arterial occlusion, gut necrosis and death
- Etiology:** The lead points may be **hyperplasia of Peyer's patches (MC)**; Meckel's diverticulum; enteric duplication cyst; small bowel lymphoma and SUBMUCOSAL lipoma.
- Affects children 4 months – 2 years
- MC cause of bowel obstruction in first 2 years of life**; usually **ileocecal**
- Presents as paroxysmal **abdominal pain**, 'currant jelly' stools (blood and mucus in stool), bilious vomiting; palpable **sausage-shaped mass**; **sign de Dance**
- Barium enema** is both **diagnostic and therapeutic**
- A/w **Henoch Schonlein purpura** and **cystic fibrosis**
- Radiology of intussusception is described in radiodiagnosis chapter (Pg 1179).**

Volvulus

- Incomplete fixation to the posterior abdominal wall, causing a **malrotated gut to twist on itself**
- Affects **children 0 to 2 years**
- Sudden onset of **pain, distension, peritonitis**, 'bird's beak' on X-ray
- Treat with surgery immediately** since gut may necrose due to **superior mesenteric A occlusion**.

Prevention of ARF

Primary prevention of ARF:

- Treatment:** When antibiotic therapy is provided **within 9 days of pharyngitis**, acute rheumatic fever can be prevented.
- Drug of choice** is **single IM injection of benzathine penicillin G**; **erythromycin** is **DOC** in penicillin allergic patients.
- Suppressive therapy**—For 12 weeks—**aspirin** (used if no carditis) and **corticosteroids** (used if carditis present or carditis + CCF present).

Secondary prevention of ARF:

- Single IM injection of Benzathine penicillin 1.2 Million units once every 3 weeks.
- Patients without proven carditis should receive prophylaxis for 5 years after last episode, or until age of 18 years (whichever is longer).
- Patients with carditis (MR or healed carditis) should receive prophylaxis for 10 years after last episode or until 25 years of age (whichever is longer).

Meconium Ileus

- In **cystic fibrosis**, meconium plug obstructs intestine preventing stool passage.

- Affects **children 0–2 weeks**; may cause **late feculent vomiting, rectal prolapse**.

PEDIATRIC RENAL CONDITIONS

Basics

- Glomerular filtration** begins at **5–9 weeks** gestation.
- A **neonate can concentrate** urine to a maximum of **700–800 mOsm/kg**, but can dilute urine to 50 mOsm/kg (like adults)
- A neonate achieves **concentrating ability** equivalent to adult by the age of **1 year**.
- 92% neonates pass urine within the first 48 hours.

CONGENITAL KIDNEY ANOMALIES

Renal Agenesis

- Syndromes** a/w Renal agenesis: Branchiootorenal, DiGeorge, Fanconi anemia, Fraser or nail patella syndromes.
- Unilateral renal agenesis** is a/w **single umbilical artery**, absent ureter, contralateral VUR and absent ipsilateral vas deferens. Unilateral agenesis is usually accompanied by **compensatory hypertrophy of the contralateral kidney** and thus should be compatible with normal renal function.
- Bilateral renal agenesis** is a/w severe **oligohydramnios**, **limb anomalies**, **abnormal Potter facies** (low set ears, flat nose, epicanthic folds and small chin), and **early death** due to **pulmonary hypoplasia**.

Multicystic Dysplastic Kidney

- Unilateral MCDK is both the **MC cystic lesion of the neonatal kidney** and **MC cause of abdominal mass in the newborn**.
- Maybe a/w **contralateral VUR or PUJ** (pelvi-ureteric junction) obstruction.
- Pathology: **Multiple, thin, walled, non-communicating** cysts of varying size in an **enlarged kidney** without identifiable parenchyma or renal pelvis.

Nephronophthisis

- Autosomal **recessive**; mutations in the **NPHP 1–9 genes encoding cystolic proteins called nephrocystins**.
- Juvenile** form is **MC**; it is the **MC inherited childhood form of kidney failure** requiring kidney replacement therapy.
- Bilateral small fibrotic** kidneys; **medullary cysts** are seen.

- Presents in 1st decade with polydipsia, polyuria or enuresis, **growth retardation** and **acidosis** and **anemia**.
- Extrarenal features: **Retinitis pigmentosa**, **hypotonia**, liver fibrosis, pancreatic dysplasia, **cerebellar ataxia** (*Joubert syndrome*), skeletal chondrodysplasia (*Jeune syndrome*), **situs inversus**.

NEPHROTIC SYNDROME

- Clinical features:
 - **Massive edema**
 - **Massive selective proteinuria** (> 2 g/day)
 - **Hypoalbuminemia** (< 2.5 g/dL)
 - **Hyperlipidemia** (> 200 mg%)
 - **Lipiduria** (lipid casts)
 - **Hypercoagulability**

Primary (Idiopathic) Nephrotic Syndrome

- MC cause in children is **minimal change disease** (*normal histology on light microscopy*)
- **Clinical features as above**
- **C3 levels are normal**; Urine—no RBCs, lipid casts and hyaline casts may be seen
- **Treatment:** Renal biopsy is not required to confirm diagnosis of minimal change disease prior to treatment. Initial longer course of **corticosteroids** (12 weeks); **relapses are common** (treat relapses for 5–6 weeks).
- Prognosis is excellent.

Steroid Resistant Nephrotic Syndrome

- Lack of remission despite treatment with prednisolone, at a dose of 2 mg/kg/day (60 mg/m²/day) for 4 weeks.
- For treatment, a combination of ACE inhibitor + any of below agents is used
 - Calcineurin inhibitors (cyclosporine, tacrolimus)
 - Cyclophosphamide.

EXTRA EDGE

- Precipitants of **acute kidney injury in nephrotic syndrome** are:
- Aggressive diuresis (excess frusemide); renal vein thrombosis
 - Prerenal volume depletion (blood loss, protracted vomiting or diarrhea)
 - Sepsis, interstitial nephritis, drugs (NSAIDs, ACE inhibitors)

Indications for Renal Biopsy in Nephrotic Syndrome

- Age < 12 months
- Gross or persistent microscopic hematuria
- Low blood C3
- Hypertension

- Impaired renal function
- Steroid resistance

Complications of nephrotic syndrome

- Hypercoagulability
- Hyperfibrinogenemia
- Peripheral arterial or venous thrombosis
- Renal vein thrombosis
- Pulmonary embolism
- Protein malnutrition
- Iron resistant microcytic hypochromic anemia (due to transferrin loss)
- Hypocalcemia
- Depressed thyroxine levels
- Susceptibility to infection (spontaneous bacterial peritonitis).

Congenital Nephrotic Syndrome

- Nephrotic syndrome presenting within first 3 months of life is congenital.
- Gene mutation a/w **congenital NS (Finnish) type** = **Nephrin** (NPHS1). ('**PH**innish = **NePH**rin = **NPHS1**!!')
- Gene mutation a/w steroid resistant NS = **Podocin** (NPHS2)

NEPHRITIC SYNDROMES

Acute Post Streptococcal Glomerulonephritis

- Following h/o **recent (1–4 weeks) group A beta hemolytic streptococcal pyoderma** (type 49) or **pharyngitis** (type 4 and 12)
- Affects boys > 3 years of age
- **Oliguria**
- **Hematuria** (smoky brown or cola colored urine)
- **Hypertension**
- **Edema**
- **Decreased C3 levels; normal C4 levels**
- **Red cell and granular casts in urine**
- **Dilutional hyponatremia**
- Fluid restriction, **furosemide**, **penicillin**, **antihypertensives**
- **> 95% have good prognosis.**
- Complication:
 - **Hypertensive encephalopathy** (headache and seizures)
 - Left ventricular failure and pulmonary edema
 - Acute kidney injury
 - Nephrotic syndrome.

Henoch-Schonlein Purpura

- **Small vessel** vasculitis with **IgA** deposition in walls of involved vessels.
- Clinically: **palpable purpura** (dorsal surface of lower extremities and buttocks) with normal platelet count; **abdominal pain**; **arthralgia**; **mesangial IgA** deposition with **glomerulonephritis**.

Renal manifestations start *within 3 months* of onset of other symptoms.

A Nephropathy

Children and young adults MC affected.
Gross hematuria usually a/w or acutely following an **URTI (MC)** or **GI** infection. In contrast to postinfectious glomerulonephritis, this feature has been called '**synpharyngitic hematuria**' since there is no significant latent period.
IgA deposition in **mesangium**; serum **complement level** is normal.

VARIOUS OTHER CONDITIONS

Vesico-Ureteric Reflux (VUR)

- VUR is the retrograde flow of urine from the bladder to the kidneys.
- MC cause of **recurrent UTI** in children; MC in **females**.
- Reflux is present since birth, detected at 2–3 years of age, BUT in **females** the age of detection is earlier.
- Children with VUR may present with **hydronephrosis** (prenatally identified using ultrasonography) OR with **clinical UTI**.
- **Micturating Cystourethrogram (MCUG)** is best investigation for VUR.

International Classification System for VUR

Grade I	Reflux into nondilated ureter (does not reach renal pelvis)
Grade II	Reflux into renal pelvis and calyces without dilated ureter
Grade III	Reflux with mild to moderate dilated ureter and minimal blunting of fornices
Grade IV	Reflux with moderate ureteral tortuosity and dilation of pelvis and calyces
Grade V	Reflux with gross dilation of ureter, pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity

PEDIATRIC HEMATOLOGIC CONDITIONS

	HUS	HSP	TTP	ITP
MC age	Children	Children	Young adults	Children or adults
Previous infection	Diarrhea (EHEC , Shigella)	URI	None	Viral (especially in children)
RBC count	↓	N	↓	N
Platelet count	↓	N	↓	↓

Management of VUR

- **Spontaneous resolution of VUR** is **common in young children** but is less common as puberty approaches
- Grade I and II—Antibiotic prophylaxis till 1 year old.
- Grade III and IV—Antibiotic prophylaxis till 5 year old; continue beyond 5 years of bowel/bladder dysfunction is present.
- Grade V—age < 1 year—antibiotic prophylaxis; age > 5 years—surgery.

Indications for Surgery in VUR

- **Breakthrough febrile UTIs** despite adequate antibiotic prophylaxis
- Severe reflux (**grade V** or **bilateral grade IV**)
- Mild or moderate reflux in females that persists as the patient approaches puberty
- Poor compliance with medications or surveillance programs
- Poor renal growth or function or **appearance of new scars**.

Posterior Urethral Valves

- MC cause of obstructive uropathy in children; occurs only in **boys**.
- May lead to end stage renal disease; VUR occurs in 50% patients.
- **Complications** include **hydronephrosis**; distended bladder with dilation of prostatic urethra; recurrent UTI and renal failure.
- '**Keyhole**' sign seen on ultrasound.
- Definitive treatment is by **endoscopic destruction of the valves** with continuing supportive treatment of the dilated urinary tract, the recurrent urinary infections and the uremia.

Contd...

Contd.

	HUS	HSP	TTP	ITP
Peripheral smear	Hemolysis	N	Hemolysis	N
Kidney effects	ARF, hematuria	Hematuria	ARF, proteinuria	None
Treatment	Supportive*	Supportive*	Plasmapheresis, NSAIDs; NO platelets**	Steroids*** , splenectomy if drugs fail, Rituximab
Key differential points	Age, diarrhea	Rash (palpable purpura), glomerulonephritis, abdominal pain, arthritis, melena	CNS changes, age	Antiplatelet antibodies

Key:

HUS = Hemolytic uremic syndrome; HSP = Henoch-Schönlein purpura; TTP = Thrombotic thrombocytopenic purpura; ITP = Idiopathic thrombocytopenic purpura; ARF = Acute renal failure; EHEC = Enterohemorrhagic *E. coli*.

* In HUS and HSP, patients may need dialysis and transfusions.

** Do not give platelet transfusion to patients with TTP, clot may form.

*** Give steroids only if the patient is bleeding.

PEDIATRIC CNS CONDITIONS

Head Malformations

Anencephaly	Due to failure of closure of the rostral neuropore
Holo-prosencephaly	Incomplete separation of the cerebral hemispheres. Seen in Patau's syndrome
Parencephaly	Cysts or cavities in the brain may result from developmental defect or acquired lesions including infarction of tissue
Lissencephaly	Bat like brain with no cerebral convolutions and a poorly formed sylvian fissure (agyria)
Schizencephaly	Unilateral or bilateral cleft in the cerebral hemispheres , microgyria
Encephalacele	Is a malformed diverticulum of CNS tissue extending through a defect in the cranium
Arnold Chiari deformity	Elongation of the cerebellar tonsils and drawing of cerebellum into the fourth ventricle; associated with myelomeningocele
Dandy Walker malformation	Enlarged posterior fossa, absent cerebellar vermis and a large midline cyst

Contd...

Contd...

Shapiro's syndrome	Agenesis of corpus callosum
---------------------------	------------------------------------

Causes of Bacterial Meningitis in Children

Neonates	Group B Streptococcus— <i>Str. agalactiae</i> is MC (GPC) E. coli is 2nd MC (GNB) <i>Listeria monocytogenes</i> (GPC)
Infants > 1 month and children	<i>Streptococcus pneumoniae</i> is MC (GPC) <i>N. meningitidis</i> (GNC)
Adults > 20 years	<i>Streptococcus pneumoniae</i> (GPC)

Haemophilus Meningitis

- ***Haemophilus influenzae B* (Hib)** meningitis primarily affects **infants < 2 years of age**.
- **Fever and altered CNS** are the MC features at presentation.
- Nuchal rigidity **may or may not be evident**.
- **Subdural effusion**, is the MC complication; convulsions are common
- **Of survivors**, 6% have **permanent sensorineural hearing loss**, and **residual auditory deficit** is common

Common Pediatric Epilepsy Syndromes

Syndrome	Symptoms	Diagnosis	Treatment
Absence seizures	Multiple brief staring episodes	Generalized 3-Hz spike and wave pattern on EEG	Ethosuximide (treats only absence seizures), valproate, lamotrigine (both are more broad spectrum)
Infantile spasms (west syndrome)	Affects infants < 1 year (3–8 months) 'Jackknife spasms' or salaam spells (sudden drooping of the head and flexion of the arms), developmental regression, mental retardation	Hypsarrhythmia on EEG. a/w tuberous sclerosis	ACTH, corticosteroids, vigabatrin is the DOC (especially in tuberous sclerosis)
Lennax Gastaut syndrome	First seizure between 1 and 7 years of age; multiple progressive difficult to treat type mixed seizures with drop attacks Intellectual regression occurs	Atypical spike and wave pattern in frontal region on EEG	No effective treatment; valproic acid tried
Juvenile myoclonic epilepsy (Janz syndrome)	Affects healthy adolescents (12–16 years) myoclonic jerks in early morning hours upon waking	Positive family history	Seizures respond well to Rx. Valproate is drug of choice and is required lifelong
Benign partial epilepsy	Partial seizures during wakefulness (oral, vocal)	Classic interictal spikes from the centrotemporal (rolandic) region	Seizures usually disappear by adolescence
Landau Klefner syndrome	Normal children and lose language between 3 and 6 years ; often confused with autism	Bilateral temporal spike and sharp waves on EEG; irreversible language loss	Antiepileptic medications

Febrile Convulsions

- Seizures during fever between 6 months and 5 years of age; frequently genetically determined.
- Convulsions are NOT related to degree of temperature but are frequent if temperature rises abruptly.

1. Simple Benign Febrile Convulsions

- They occur **within 24 hours of onset of fever**
- Last < **10 minutes** and are usually **single per febrile episode**
- Convulsions are **generalized**
- **NO post-ictal** neurological deficit
- **Family history** may be present.

2. Atypical Complex Febrile Convulsions

- Lasts for more than 15 minutes and is focal in nature
- Treatment of 'central' precocious puberty—GnRH analog (Leuprolide), monthly IM injections.

Treatment

- Antipyretics (paracetamol, ibuprofen; **AVOID aspirin due to risk of Reye's syndrome**)
- Hydrotherapy, tepid sponging, oxygen.
- IV **diazepam** or phenobarbitone for control of seizures.

- EEG, lumbar puncture NOT recommended for first episode.

Prophylaxis

- **Intermittent prophylaxis** indicated if **3 or more febrile seizures in 6 months OR 6 or more in 1 year**; febrile seizures **lasting more than 15 minutes** or **requiring drug therapy** to control seizures. **Oral clobazam** is an effective prophylactic.
- **Continuous prophylaxis**—indicated in event of failure of intermittent prophylaxis, and in recurrent atypical seizures. Only **sodium valproate or phenobarbitone** are effective; **carbamazepine and phenytoin** are **NOT effective**.

Risk of recurrence of febrile seizures

- Family h/o febrile seizures
- First seizure before 1 year of age
- Brief duration (< 1 h) between onset of recognized fever and seizure
- Low temperature (the lower the fever at onset of seizure, the higher the risk of recurrence); initial temperature > 40°C is a/w a **decreased risk of recurrence**
- Complex seizure
- Neurodevelopmental retardation

CEREBRAL PALSY

- **Cerebral palsy (CP)** is a nonspecific term used to describe a chronic, static impairment of muscle tone, strength, coordination or movements.
- The term implies that the condition is **nonprogressive** and originated from some type of **cerebral insult or injury before birth, during delivery, or in the perinatal period.**
- Spastic CP: The MC form of CP (75% of cases) involve spasticity of the limbs. A variety of terms denote the specific limb or combination of limbs affected: monoplegia (one limb); hemiplegia (arm and leg on same side of body, but arm more affected than leg); paraplegia (both legs affected with arms unaffected); quadriplegia (all four limbs affected arms > legs).
 - **Spastic hemiplegia:** Due to large vessel **MCA stroke.** Spasticity seen on one side of body arms > legs > face.
 - **Spastic diplegia:** A/w **prematurity;** bilateral spasticity of arms > legs; resulting in lagging of legs while crawling (**commando crawling**); **periventricular leukomalacia** is characteristic.
 - **Spastic quadriplegia:** A/w **birth asphyxia; scoliosis** may occur.
- Ataxic CP
- Hypotonic CP
- Extrapyrimal (athetoid) CP.

PEDIATRIC ENDOCRINE CONDITIONS

Precocious Puberty

- Precocious puberty is defined as the **onset of secondary sexual characters before 8 years of age in girls and 9 years in boys** (or **menarche before 10 years**).

Gonadotropin-dependant or 'True' or central precocious puberty	Gonadotropin-independant or peripheral precocious puberty (pseudopuberty)
<ul style="list-style-type: none">• Due to hypothalamic-pituitary-gonadal activation<ul style="list-style-type: none">- Idiopathic- CNS tumors (hamartoma, pituitary adenoma, craniopharyngioma, glioma)- CNS infections (TB, meningitis)- CNS trauma- CNS malformations (arachnoid cyst, hydrocephalus, septo-optic dysplasia)	<ul style="list-style-type: none">• NO hypothalamic-pituitary-gonadal activation.<ul style="list-style-type: none">- Exogenous sex steroid exposure (estrogen, testosterone)- Congenital adrenal hyperplasia- Adrenal tumor- Testicular tumor (seminoma, germinoma, leydig cell tumor)- Ovarian estrogen (cyst, tumor, aromatase excess)- HCG secreting tumor- McCune Albright syndrome- Activating LH receptor mutation

EXTRA EDGE

- **Delayed puberty in girls:** If there are no pubertal signs by age 13 years (failure of breast budding) or menarche by 16 years.
- **Delayed puberty in boys:** If no secondary sexual characteristics develop by 14 years of age or if more than 5 years have elapsed since the first signs of puberty without completion of genital growth.
- **Puberty tends to be delayed in hypothyroidism** although precocious puberty has been described in longstanding severe hypothyroidism.
- Treatment of 'central' precocious puberty—GnRH analog (**Leuprolide**), monthly IM injections.

Congenital Hypothyroidism

- MC cause is **thyroid dysgenesis (aplasia/hypoplasia).**
- The majority of infants **appear normal at birth.**
- Clinical features include **prolonged** physiological jaundice, feeding problems, **hypotonia, enlarged tongue, delayed bone maturation, delayed dentition, constipation** and **umbilical hernia.**
- **Wide open cranial sutures** and **posterior fontanelle** is one of the **earliest** clinical signs.
- **Cretinism** is a condition of **severely stunted physical and mental growth** due to untreated congenital deficiency of thyroid hormones (congenital hypothyroidism) usually due to **maternal hypothyroidism.**
- **Kocher-Debre-Semelaigne syndrome:** Calf muscles are hypertrophied and returns to normal after treatment of congenital hypothyroidism.
- **Neonatal thyroid screening for T4 and TSH is most sensitive**—Usually done **after 72 hours** (between day 2–4, to avoid physiological neonatal TSH surge).

DISORDERS OF SEX DIFFERENTIATION

How does normal sex differentiation occur?

- **In absence of Y chromosome**
 - Germinal tissue differentiates into ovaries
 - Wolffian (mesonephric) duct structures undergo apoptosis.
- **In presence of Y chromosome**
 - Germinal tissue differentiated into testis
 - Mullerian inhibitory factor (**MIF secreted by Sertoli cells**) causes Mullerian tissue to undergo apoptosis
 - Fetal **testosterone** develops the Wolffian duct structures (epididymis, seminal vesicles and **vas deferens**)
 - **5-alpha reductase** converts testosterone to dihydrotestosterone (DHT)
 - **DHT** develops the **prostate gland and male external genitalia.**

True hermaphrodite	Pseudohermaphrodite
<ul style="list-style-type: none">• Fetus has both male and female gonads• Usually 46, XX	<ul style="list-style-type: none">• Male pseudohermaphrodite: XY with testis BUT phenotypically female (testicular feminization)• Female pseudohermaphrodite: XX with ovaries BUT phenotypically male (virilisation in congenital adrenal hyperplasia—MC cause)

Congenital Adrenal Hyperplasias

- Also called **adrenogenital syndrome** is an **autosomal recessive** disorder caused by deficiency of enzymes involved in synthesis of steroid hormones in adrenal cortex.
- All steroid hormones are derived from precursor pregnenolone which is in turn derived from cholesterol.

21-Hydroxylase Deficiency

- 21- α -hydroxylase deficiency is the MC type
- Classic salt wasting form**
 - \downarrow cortisol (increased ACTH), \downarrow mineralocorticoids, \uparrow sex hormones.
 - Clinically: masculinization, female pseudohermaphroditism
 - **Hypotension, HYPOnatremia, hyperkalemia, \uparrow plasma renin activity and volume depletion (Hypovolemic shock).**
 - Hypoglycemia.
- Classic Simple Virilising form**
 - Clinical features are due to overproduction of androgens.
 - BP is normal and there is no salt wasting.

EXTRA EDGE

- All CAH are characterized by an enlargement of adrenal glands due to \uparrow ACTH stimulation because of \downarrow levels of cortisol.

Congenital adrenal hyperplasia (adrenogenital syndrome)	Testicular feminization (androgen insensitivity) syndrome
46 XX; normal ovaries	46, XY chromosome
Masculinization of external genitalia (excessive production of androgen by the fetal suprarenal glands) causing various degrees of clitoral hypertrophy and partial fusion of labia majora	Female external genitalia (insensitivity to androgens secreted by the interstitial cells of testes) with well developed breasts
Persistent urogenital sinus	Most testes contain bilateral hamartomas; testis in the abdomen or inguinal canals
	Absence of uterus, tubes and vagina upto hymen due to secretion of mullerian inhibiting substance by the sertoli cells of testis

THE 'ORIGINAL' SIX EXANTHEMATOUS ILLNESSES

- | | |
|--------------------------|---------------------------------------|
| 1. First disease | : Measles |
| 2. Second disease | : Scarlet fever |
| 3. Third disease | : Rubella (German measles) |
| 4. Fourth disease | : Dukes disease (scarlatinella) |
| 5. Fifth disease | : Erythema infectiosum |
| 6. Sixth disease | : Exanthem subitum (Roseola infantum) |

Measles (Rubeola, First Disease)

- Caused by RNA **paramyxovirus**; **onle one antigenic type** of measles virus is known.
- IP = 8–12 days
- Spread by **airborne droplets** from nose and throat secretions of a case of measles, usually 4 days before and 5 days after the appearance of the rash.
- Carriers do NOT occur.
- **Secondary attack rate is 90%.**
- Incubation period (IP)= 10–14 days; i.e., 10 days for exposure to onset of fever and 14 days to appearance of ras; IP for live vaccine virus is 7 days.
- Affects preschool children aged **6 months–3 years** of age.
- Measles shows cyclic trend with epidemics every 2–3 years.
- One attack of measles generally confers **lifelong immunity**; maternal antibodies protect infants up to 6 months of age.
- **Mortality 400 times higher** in the malnourished child (also vit. A. deficiency).

Stages of chickenpox

- **Prodromal Stage:**
 - Last 4 days (from days 10–14 after infection), characterized by fever, coryza, dry hacking cough, conjunctivae look glassy, and then the semilunar fold swells (**Meyer's sign**).
 - **Koplik's spots:** Are 1–2 mm bluish-white spots on a red base on the buccal mucosa opposite the **lower second molars, pathognomonic** of measles, generally seen on **2nd or 3rd day** of symptoms and are often fading as the rash appears.
 - **Comby's sign:** Thin, **whitish patches on the gums and buccal mucosa** formed of degenerated squamous epithelium.
- **Eruptive stage:**
 - On the fourth/fifth day, the macular rash appears consisting of discrete **lesions that begins behind the ears** and become confluent as **rash spreads from hairline downward, sparing palms and soles**
 - Rash and fever disappear in 3–4 days signaling the end of the disease.
 - Prolonged fever suggests a complication of measles. The entire illness lasts **about 10 days.**
- **Post measles stage:**
 - Weight loss, susceptible to infections, growth retardation, diarrhea, cancrum oris, reactivation of pulmonary TB, malnutrition (vitamin A deficiency—keratomalacia and xerophthalmia).

• Complications

- **Respiratory:** *Otitis media (MC)*; bronchopneumonia - *giant cell (Hecht) pneumonia*; MC cause of death is *pneumonia*.
- **Neurological:** **Most serious**; febrile fits, meningitis, *encephalitis (1 in 1000 cases)*, *subacute sclerosing panencephalitis* (occurs 1-3 years later and **very rare**, 1 in 3,00,000 cases).
- **Digestive:** Resistant diarrhea, achlorhydria, hepatitis, appendicitis.
- **Miscellaneous:** Myocarditis, glomerulonephritis, thrombocytopenic purpura, tuberculin anergy, keratoconjunctivitis sicca, intrauterine infection may cause fetal malformations.

• Diagnosis

- Serology for measles **IgM antibody**. **Warthin-Finkeldy** cells are multinucleate **giant cells** with inclusion bodies in the nucleus and cytoplasm, found in lymphoid tissues in prodromal stage, **pathognomonic** of measles.

• Treatment

- **Isolate** the patient; treat any secondary bacterial infection; **vitamin A prophylaxis** (1 lakh units below 1 year and 2 lakh units above 1 year).

• Prevention

- **Measles vaccine:** See under PSM chapter under 'Vaccines' section (Pg 460).
- **Measles immunoglobulin:** WHO recommended dose is 0.25 mL/kg and should be given **within 3-4 days** of exposure to prevent the disease.

Chickenpox (Varicella)

- Caused by **Varicella-zoster virus (VZV)** also called human (**alpha**) **herpes virus 3**; only one antigenic type of VZV is known.
- Source of infection is usually a case of chicken pox.
- Spread by **respiratory droplets** and from the **vesicular fluid during the first 3 days** of the illness. The **scabs** are **NOT** infective.
- **Period of infectivity** is from 1-2 days before the appearance of the rash and 4-5 days thereafter.
- **Secondary attack rate** is **90%**. One attack usually gives **immunity for life**.
- Affects children in age group of **5-9 years**.
- **Presentation**
 - Incubation period = 15 days (10 to 21 days).

Stages of chickenpox

- **Pre-eruptive stage:**
 - Fever, malaise, shivering and back pain.
- **Eruptive stage**
 - **Rash** comes on the day the fever starts. It is **centripetal** in distribution; **symmetrical**; **superficial**, first appears on the **trunk**; **mucosa** is also involved, affects axilla BUT **palms and soles** are spared.
 - The rash advances quickly through the stages of macule, papule, vesicle, pustule and scab (**pleomorphic pruritic rash**).
 - Vesicles are **unilocular**—'Dew drops on Rose petal' appearance.
 - Evolution of rash is very **rapid** and scabs begin to form 4-7 days after rash appears.
 - **Temperature rises** with each fresh crop of rash.

• Complications

- Secondary bacterial infection of the rashes (**MC complication**);
- **Varicella pneumonia**—MC complication in neonates, adults and immunocompromised patients.
- Hemorrhages into the lesion; encephalitis, **acute cerebellar ataxia**; **purpura fulminans**; arthritis; hepatitis; glomerulonephritis; **Reye's syndrome**, **thrombocytopenia**.
- Recovery from primary infection is commonly followed by the establishment of latent infection in the sensory ganglia often without clinical manifestations—reactivation from dorsal root ganglia leads to **Herpes zoster**.

• Diagnosis

- **Rapid** method—direct immunofluorescence.
- **Confirmatory** test—VZV DNA detection by PCR (anti-VZV IgM antibody is NOT the method of choice).

• Treatment

- Symptomatic and supportive, since this is a **self-limiting** condition. **Aspirin should NOT** be used (may increase the risk of developing **Reye's syndrome**).

• Neonatal/fetal varicella

- Perinatal transmission of **VZV across the placenta** infects the fetus - causes **cicatricial skin lesions**, **limb hypoplasia** or paresis, **microcephaly**, chorioretinitis, deafness and cerebrocortical atrophy.

• Prevention

- **Live attenuated** chicken pox vaccine of **Oka strain** is now available.
- Indicated in children between **12 and 18 months**.
- Not recommended in National Program.
- Given as 0.5 mL SC injection; two doses at 15-18 months and 4-6 years.

- Store in dark at 2-8°C and use within 30 minutes of reconstitution.
- **Varicella zoster immunoglobulin**, 1.25 to 5 mL IM given within 72 hours of exposure will modify or prevent the disease. Reserved for immunosuppressed contacts of acute cases and newborn contacts.

Rubella (German Measles, Third Disease)

- Caused by **Togavirus**, an **enveloped RNA virus**; only **one serotype** of rubella virus exists.
- Transmitted by (1) droplet infection through respiratory route or (2) transplacental vertical transmission.
- Incubation period = 2 to 3 weeks (average **18 days**).
- The patient is infective 7 days before and 7 days after the day the rash starts.
- Mainly a disease of childhood (3-10 years); BUT in developed countries, 70% cases are > 15 years of age.
- **Postnatal Rubella**
 - Postauricular, cervical and suboccipital **lymphadenopathy** (may appear as early as 7 days before the appearance of the rash).
 - **Macular rash** appears **first on face**; spreads from hairline downwards, clearing as it spreads. The rash **disappears altogether by the third day**.
 - **Forschheime spots** (palatal petechiae), also seen in scarlet fever and infections mononucleosis.
 - The most widely used serological diagnostic test is the **hemagglutination inhibition** test.
 - Treatment: Usually none needed, self-limiting.
 - Complications: **Arthritis** especially among women, **encephalitis**, **thrombocytopenic purpura**, malformations **in utero**.

Congenital Rubella

- Occurs due to maternal infection during the **first trimester** of pregnancy (maximum fetal transmission if infected between 6 and 8 weeks); infection after 16 weeks causes no major abnormalities.
- Classic triad of congenital rubella syndrome = **Cataract**; **Congenital heart disease (PDA MC)**, others are pulmonary stenosis, pulmonary artery hypoplasia and VSD; **deafness** (sensorineural—MC clinical finding/MC sequel).
- Skin lesion of congenital rubella = **Blueberry muffin** lesions; thrombocytopenic purpura.
- Other features: Glaucoma, **salt and pepper** chorioretinopathy, microcephaly, cerebral palsy, IUGR, hepatosplenomegaly, motor retardation.
- IgM in blood at birth is diagnostic

Erythema Infectiosum (Fifth Disease)

- Cause: **Human parvovirus B19**, primarily affects children **5-15 years** old.

- Manifests as a **bright-red 'slapped cheek' appearance** (a raised, fiery flush on the cheeks), followed by a diffuse lacy reticular rash (on the limbs) that waxes and wanes over 3 weeks.
- Rash appears **1 week after defervescence** (disappearance of fever).
- Adults with fifth disease often have **arthritis**, and **non-immune fetal hydrops** can develop in association with this condition in pregnant women.
- **Parvovirus B19** is also the cause of **aplastic crises in sickle cell disease**.

Exanthem Subitum (Roseola Infantum, Sixth Disease)

- Cause: **Human herpes virus 6 (HHV-6B)**.
- MC in children **6 months-3 years** of age.
- Prodromal symptoms—URTI, conjunctival redness; **cervical or occipital lymphadenopathy**.
- As in erythema infectiosum, rash usually appears after fever has subsided.
- It is a **rose-pink** maculopapular rash (sparing face); resolves within 2 days **without any pigmentation or desquamation**.
- **Nagayama's spots** are erythematous papules at the uvulo-palatoglossal junction seen in roseola infantum.

TORCHES INFECTIONS

- **TO**xoplasmosis
- **R**ubella
- **C**ytomegalovirus
- **H**erpes
- **S**yphilis
 - **Live attenuated RA 27/3Q vaccine**, produced in human diploid fibroblast; given 0.5 mL SC injection.
 - Seroconversion occurs in more than 95%; pregnancy is considered a contraindication to rubella immunization.
 - Priority groups for rubella vaccination in India:
 - I priority—15-34 years old females
 - II priority—all children aged 1-14 years
 - III priority—routine immunisation of all children aged 1.

CONGENITAL TOXOPLASMOSIS

- Congenital infections develop only when the nonimmunized mother develops pregnancy or infection < 6 months before pregnancy.
- Prevention: **Avoid exposure to cats** and cat feces during pregnancy; avoid **raw undercooked meat**.
- The incidence of transplacental infection is lowest in first trimester but the **disease in neonates is most severe**.

- The incidence of **transplacental infection is highest in III trimester** (after 6 months) but the infant is not severely affected.

- Triad of 3 'C' = **Chorioretinitis** (MC), **Convulsions** and intracerebral **Calcification** (ring enhancing lesions on CT scan).
- Other features are **hydrocephalus** or **microcephaly**, **microphthalmia**, **mental retardation**, **deafness**, **blindness**, **thrombocytopenia**, **anemia**, **nephritic syndrome** and **optic atrophy**.

- Diagnosis is by **serological** tests. These are:

- **Anti-toxoplasma IgG** in infants blood does NOT confirm the diagnosis, because maternal IgG can easily cross the placenta; disappears by 6–12 months of age. Serological tests to detect IgG:

- **Sabin-Fieldman** dye test (most preferred IgG test and gold standard).
- IgG IFA test (IgG indirect fluorescent antibody test).
- Differential agglutination (AC/HIS) IgG test
- Avidity test: It measure the strength of antigen-antibody reaction for IgG antibody.

- **Anti-toxoplasma IgM** does not cross the placenta; therefore, IgM is the **test of choice for determining congenital infection**. Serological tests for IgM are:

- IgM IFA (Indirect fluorescent antibody test)
- Double sandwich enzyme linked immunosorbent assay: More sensitive than IgM IFA.
- Immunosorbent agglutination assay (ISAGA)

- Anti-toxoplasma IgA may have **greater sensitivity for neonate** compared to IgM assay. Serological tests for IgA are:

- Double sandwich enzyme linked immunosorbent assay (IgA ELISA): It is better than double sandwich IgM ELISA for diagnosis of congenital toxoplasmosis.
- The immunosorbent agglutination assay (ISAGA) IgA.

- Prevention: **Spiramycin** is given during pregnancy to prevent vertical transmission of toxoplasma.

CONGENITAL CMV INFECTION

- CMV is the MC cause of congenital infection.
- It leads to **cytomegalic inclusion disease**. Most infection are asymptomatic.
- **Petechia**, **hepatosplenomegaly** and **jaundice** is the **classical triad** of presentation. Other important features are **microcephaly**, **periventricular calcification**, **IUGR**, **chorioretinitis**, **thrombocytopenia**, **inguinal hernia**, and **seizures**.

- Sequelae—hearing loss, mental retardation, visual impairment.

Diagnosis

- **Virus Isolation of CMV** is the definitive **diagnostic** method. Specimens may be urine (urine cultured), saliva, blood (buffy coat), bronchoalveolar washing or amniotic fluid.
- The MC method of detection is quantitative nucleic acid testing (QNAT) for CMV by polymerase chain reaction (PCR).
- Serology is NOT very helpful, IgM test lacks sensitivity and specificity. IgG tests are not diagnostic in IgG antibodies can cross the placenta (may be maternal infection).
- PCR for viral genome (DNA) may be used.
- In histopathologic examination, CMV infected cells contain **large intranuclear and small intracytoplasmic inclusion bodies** ('owl-eye' inclusions), which are pathognomonic.

NEONATAL HSV INFECTION

- MC caused by **HSV-2** (only 30% by HSV 1).
- Case fatality rate exceeds 60% in untreated neonatal herpes.
- The infection is **acquired by passage through an infected genital tract** with birth. The **greatest risk**, i.e. 50% transmission rate occurs with a primary infection on the mother **at time of delivery** (because the antibodies have not developed, there is more virus present and no antibody transfer).
- Perform a **C-section if mother has active lesions at time of delivery**.
- Neonatal infections present on the **6th day postpartum**. There are 3 major categories: Localized skin, eye and mouth infection; CNS infection; disseminated infection.
- The hallmark of neonatal HSV infection—the **vesicular, ulcerative skin lesions** occurs in only 30–43% children.
- If left untreated, the virus dissemination can occur to internal organs which are the most serious complication of neonatal herpes.

CONGENITAL SYPHILIS

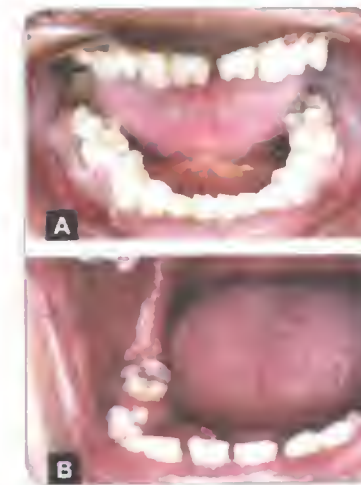
- **Early manifestations**, which appear within the first 2 years of life (often at 2–10 weeks of age), are infectious, and resemble the manifestations of severe secondary syphilis in the adult.

Early manifestations of congenital syphilis

- **Rhinitis**, or '**snuffles**' (**earliest sign** appearing 2–6 weeks after birth)
- **Bullae (syphilitic pemphigus)**, **Vesicles**, **superficial desquamation**, **petechiae**, and (later) **papulosquamous lesions**, mucous patches, and **condylomata lata**
- Bone changes: **osteochondritis (Parrot's pseudoparalysis)**, **osteitis** and **perostitis**
- **Thrombocytopenia**
- **Pneumonia alba** (white lung)
- **Hepatosplenomegaly**
- **Lymphadenopathy**
- **Anemia**, **leukocytosis**
- **Jaundice**

- **Late manifestations**, which appear after 2 years and are noninfectious and is largely subclinical—characterized by:

- **Interstitial keratitis**
- **Bilateral knee effusions (Clutton's joints)**
- **Periostitis**
- **Eighth nerve deafness**
- **Recurrent arthropathy**
- **Destruction of hard palate and bony nasal septum.**
- **Residual stigmata: Classic stigmata include**
 - **Hutchinson's teeth** (centrally notched, widely spaced, peg-shaped upper central incisors)
 - **'Mulberry' molars** (sixth-year molars with multiple, poorly developed cusps).
 - **Saddle nose** and
 - **Saber shins (Saber tibia)**
 - **Rhagades**: Wrinkled radiating scars around the mouth
 - **Olympian brow** - prominent forehead due to periostitis of frontal bone



Figs 19.16A and B: Hutchinson's teeth. Hutchinson's **A**, incisors; **B**, molars

EXTRA EDGE

- **Hutchinson's triad:** sensorineural deafness; interstitial keratitis; Hutchinson's teeth (central notched peg shaped incisors).

WILMS TUMOR

- MC renal **malignancy** of early childhood (2–4 years).

Wilms tumor syndrome

- **WAGR** – Wilms tumor, Aniridia, Genital anomalies, mental Retardation (**11p13**).
- **Denys-Drash syndrome** (gonadal dysgenesis and congenital nephrotic syndrome leading to renal failure, mutation in the WT-1 gene).
- **Beckwith-Wideman syndrome** (enlargement of body organs, hemihypertrophy, renal medullary cysts, adrenal cytomegaly).

- Histopathology: This tumor displays a classic **triphasic** histology with **blastemal (B)**, **stromal (S)**, and **epithelial (E)** features.
- Huge **palpable flank mass**, **hemihypertrophy**, **hematuria**, **hypertension**.
- Diagnosis by **CT/ultrasound** and **confirm by excisional biopsy**.
- Treatment: **transabdominal nephrectomy** followed by chemotherapy (vincristine, dactinomycin)—started before discharge by postop **day 5**; prognosis is usually good.
- Wilms tumor is **highly radiosensitive**, postoperative radiotherapy should be given **within 10 days** after surgery.

NEUROBLASTOMA

- MC tumor of **adrenal medulla** but can occur anywhere along sympathetic chain; affects children < 5 years.
- Risk factors: **N-myc** oncogene; **Neurofibromatosis**, **tuberous sclerosis**, **pheochromocytoma**, **Hirschsprung's disease**.
- Clinically: abdominal mass, hepatomegaly, leg edema, HTN (**less likely**), **periorbital bruising**.
- In 90% of cases of neuroblastoma, elevated levels of **catecholamines** or its metabolites (**dopamine**, **homovanillic acid (HVA)**, and/or **vanillylmandelic acid (VMA)**) are found in the urine or blood.
- Treatment: Localized tumors cured with excision; chemotherapy and radiotherapy can be used as adjunct.
- Good prognosis if diagnosed < 1 year of age. **Shimada histological classification** is used.
- **Dinutuximab** used for treatment of pediatric patients with high risk neuroblastoma.



Fig. 19.17: Left-sided adrenal neuroblastoma with secondaries in orbit. Note scar of left-sided adrenalectomy

D/D of Wilms Tumor, Abdominal Neuroblastoma

	Wilms tumor	Neuroblastoma
Age in years	2–5	<2 years, 30% under 1 year
Health	Well	Usually ill, lethargic
Clinical	Swollen abdomen	Pale, weight loss, diffuse bone pain
Mass	Lobulated	Irregular edge, craggy hard
Crosses midline	Rare	Common
Bilateral	Rare	Occasional
IVP: Renal pelvis	Grossly distorted	Pushed down by mass above
Calcification	10% cases	Common in 90% cases
Metastases	Lungs	Bone (orbits classically)

EXTRA EDGE

Most common pediatric malignancy

- **First:** Leukemia
- **Second:** Brain tumors
- **Third:** Lymphoma

BREASTFEEDING AND BREAST MILK

Cardinal Principles of Breastfeeding

- Breastfeeding should be initiated *within 1 hour after birth*.

- WHO recommends exclusive breastfeeding during the **first 6 months of life** (except vitamin drops where indicated)—has the potential to *reduce under-5 mortality rate by 13%*.
- **Weaning/complementary feeding** should start by **6 months** of age and breastfeeding should be continued for **up to 2 years**.

Mean Output of Breast Milk Per Day

Months of Lactation	Mean output (mL)
0–2	530
3–4	640
5–6	730
7–8	660
9–10	600
11–12	525

Special Features of Breast Milk

- **Proteins:** Breast milk protein contains approximately **75% whey proteins, largely lactalbumins and lactoglobulin which are easily digested**, and only 25% casein (*in cow's milk casein is the main protein!*).
- **Amino acids:** Breast milk has amino acids like **taurine and cysteine** which are necessary for neurotransmission and neuromodulation.
- **Fats:** Breast milk is **rich in long chain polyunsaturated fatty acids (DHA—Docosahexaenoic acid)** necessary for the myelination of the CNS.
- **Carbohydrates:** Rich in **lactose**.
- **Electrolytes:** **Osmolality of breast milk is low** presenting a low solute load to the neonatal kidney.
- Spermine, spermidine and putrescence: Important in cell growth and differentiation.
- **Water content** of breast milk is **88%**—hence newborn does not require additional water in first few months of life.
- Anti-infectives in breast milk:
 - **Antimicrobial agents:** Macrophages, lysozymes, complements, Immunoglobulins (secretory IgA protects respiratory and GI tracts)
 - **PABA**—para-aminobenzoic acid **protects against malaria**
 - **Lactoferrin:** Bacteriostatic against enterobacteria, *E.coli*
 - **Peroxidases:** Kill bacteria
 - **Bile duct stimulated lipase:** Lyses ameba and giardia
 - **Bifidus factor:** Helps in colonization of *lactobacillus bifidus* which helps in digestion.

- **Others:** Breast milk also has **IgA, lysozyme, bifidus factor, interferon, macrophages, lymphocytes** and other protective substances.
- Breastfed baby is likely to have an **IQ of 8 points higher** than a nonbreastfed baby.

Storage of Breast Milk

- **Expressed breast milk** can be stored:
 - At **room temperature**—for 6–8 hours
 - In **refrigerator**—for 24 hours
 - In **freezer** at 20°C for 3 months

Composition of Breast Milk

1. **Colostrum:** Milks secreted during first 3–4 days after delivery; its yellow, thick and contains large amounts of antibodies and vitamins A, D, E and K; BUT has less fat and sugar.
2. **Transitional milk:** From 3–4 days to 2 weeks after delivery; fat and sugar content increases.
3. **Mature milk:** Thinner and watery.
4. **Preterm milk:** Milk of mother who delivers before 37 weeks.
5. **Foremilk:** Milk secreted at start of a feed. It is watery and rich in proteins, sugars, minerals, vitamins and water that quenches the baby's thirst.
6. **Hind milk:** Milk secreted at end of feed; it is richer in fat, hence, provides more energy and gives a sense of satiety (satisfies baby's hunger).

Breast Milk vs Cow's Milk

- **Higher than cow's milk:** Lactose; lactalbumin, lactotransferrin, immunoglobulin, lysozyme, carbohydrates (especially lactose), iron, vitamins C and D.
- **Lesser in breast milk:** **Proteins;** fat and minerals (**calcium, phosphorus and sodium**).
- The **coefficient of uptake of iron** in breast milk is **70%**.
- **REMEMBER:** **Goat's milk is deficient in vitamin D, vitamin B12, iron and folic acid**; hence **megaloblastic anemia** may be seen if exclusively goat's milk is given!

Differences between Human Breast Milk and Cow's Milk

Constituent	Breast milk (g/100 mL)	Cow milk (g/100 mL)
Proteins(g)	1.1	3.3
Carbohydrates(g)	7.0	5.0
Lactose(g)	6.2	5.0
Fats	3.4	4.1
Minerals(g)	0.2	0.8

Contd...

Constituent	Breast milk (g/100 mL)	Cow milk (g/100 mL)
Calcium(mg)	28	120
Phosphorus(mg)	11	90
Energy	640 Kcal	650 Kcal
Amino acids	Rich in cystine, taurine	Rich in methionine

Kangaroo Mother Care (KMC)

- KMC introduced by **Dr Hector Martinez** and **Dr Edzer Ray** in **Colombia** in 1979.
- KMC is a special way of caring of **low birth weight (LBW)** babies. In KMC, the baby is continuously kept in **skin-to-skin contact** by the mother and **breastfed exclusively** to the utmost extent; KMC is initiated in the hospital and *continued at home*.

Criteria for Eligibility

- KMC is indicated in all stable LBW babies (>1800 g).
- < 1800 g babies should be stabilized before KMC can be given
- KMC can be given even when IV fluids or oxygen therapy is being given and even with orogastric tube in place.

Benefits of KMC

- **Increased breastfeeding rates.**
- **Increased duration** of breastfeeding.
- Effective **thermal control** with a **reduced risk of hypothermia**.
- KMC cared LBW infants could be **discharged from the hospital earlier**.
- **Less morbidity.**



Fig. 19.18: Kangaroo mother care

Contd...

- Less predisposition to apnea.
- Protects against nosocomial infections and even after discharge from the hospital, KMC is a/w reduced incidence of severe illness including pneumonia during infancy.
- Mothers are *less stressed* and report a *stronger bonding* with the baby.
- KMC can be stopped when the baby attains a weight of 2500 grams and a gestational age of 37 weeks.

EXTRA EDGE

- **Nipple confusion:** A baby is said to have nipple confusion when he finds it difficult to latch on and breastfeed because he is previously had a bottle teat to suck on.

MALNUTRITION

Classifications of Malnutrition

1. **Gomez classification:** This is based on *weight retardation* (not on height retardation); the child's weight is compared with a 'normal' reference child (*50th percentile of Boston standards*) of the same age; it is useful for population screening and public health evaluations.

Weight for age (%) = {weight of patient/weight of 'normal' child of same age} × 100

Weight for age (%)	Grade of malnutrition
90–110	Normal
75–89	Grade I, mild malnutrition
61–74	Grade II, moderate malnutrition
< 60	Grade III, severe malnutrition

2. **Wellcome trust classification:** Evaluates the child for edema and with the Gomez classification system.

Weight for age (% of median)	With edema	Without edema
60–80	Kwashiorkor	Undernutrition
< 60	Marasmic Kwashiorkor	Marasmus

3. **Waterlow's classification:** Based on *stunting* (low height for age H/A) and *wasting* (low weight for height W/H)

> m - 2 SD (W/H)	< m - 2 SD (W/H)	> m - 2 SD (H/A)	< m - 2 SD (H/A)
Normal	Wasted	Normal	Stunted

If both (W/H) and (H/A) are < m - 2 SD, the child is 'wasted AND stunted'.

- a. Drop in height for age (< 90%) = **Stunted**
- b. Drop in weight for height (< 80%) = **Wasted**
- c. Drop in weight for age (< 80%) = **Under weight**

4. **IAP (Indian Academy of Pediatrics) classification** Based on weight for age.

Grade of malnutrition	Weight for age and severity
	> 80%, normal
Grade I	71–80%, mild
Grade II	61–70%, moderate
Grade III	51–60%, severe
Grade IV	< 50%, very severe

5. **WHO classification of undernutrition**

	Moderate undernutrition	Severe undernutrition
Symmetrical edema	No	Yes
Weight for height (measure of wasting)	Z score of -2 to -3 (70–79% of expected)	Z score < 3 (< 70% of expected)
Height for age (measure of stunting)	Z score of -2 to -3 (85–89% of expected)	Z score < 3 (< 85% of expected)

Note: Z score = standard deviation (SD) score

6. **Classification of PEM based on Body Mass Index (BMI)**

BMI	Level of malnutrition
> 20	Normal
18.5–20	Marginal
17–18.4	Mild malnutrition
16–16.9	Moderate malnutrition
< 16	Severe malnutrition

7. **Etiological classification**

- Primary malnutrition: Due to primary lack of food
- Secondary malnutrition: Due to chronic disease or causes other than lack of food.

Assessment of Severe Acute Malnutrition (SAM)

6–59 months	< 6 months
MUAC (Mid Upper Arm Circumference) < 110 mm	Visible wasting
Weight for height Median (WHM) < 70%	WHM < 70% or < -3 SD
Weight for height Z score (WHZ) < -3 SD	Bipedal edema
Bipedal edema	

Grading of Edema in Children

Grade +	Mild—both feet/ankles
Grade ++	Moderate—both feet plus lower legs, hands or lower arms
Grade +++	Severe: generalised edema including feet, legs, hands, arms and face

Contd...

Indicator	Interpretation	Comment
Wasted	Low weight-for-height (being dangerously thin for one's height)	Suggests acute malnutrition , the result of more recent food deficit or illness
Under-weight	Low weight-for-age	Combined Indicator to reflect both acute and chronic malnutrition
Hidden hunger	Micronutrient malnutrition	Deficient in vitamins and minerals

Indicators of Undernutrition

Indicator	Interpretation	Comment
Stunted	Low height-for-age (being too short for one's age!)	Indicator of chronic malnutrition , the result of prolonged food deprivation and/or illness

Contd...

Protein Energy Malnutrition

	Marasmus	Kwashiorkor
Clinical setting	• Decreased energy intake	• Decreased protein intake during stress state
Time to develop	• Gradual (months or years)	• Rapid (Weeks)
Occurrence	• More common	• Less common
Edema	• Absent	• Present
Activity	• Active	• Apathetic
Liver enlargement	• Absent	• Present
Appetite	• Good	• Poor
Clinical features	• Starved appearance • Mankey facies (like thin old man) and baggy pants (skin of buttocks hanging down)	• Well-nourished (sugar baby) appearance • Easy hair pluckability • Flaky Paint dermatosis • Flag sign (alternate bands of hypopigmented and normal hairs) • Pitting edema
Laboratory findings	• Creatinine-height index < 60%	• Total iron-binding capacity < 200 microg/dL • Lymphocytes < 1500/microL • Anergy
Recovery	• Early recovery	• Slow recovery
Infections	• Less prone	• More prone
Mortality	• Less	• High
Diagnostic criteria	• Triceps skinfold < 3 mm • Mid-arm muscle circumference < 15 cm	• Serum albumin < 2.8 g/dL • At least one of the following: – Poor wound healing, decubitus ulcers, or skin breakdown – Easy hair pluckability – Edema



Fig. 19.19: Marasmus



Fig. 19.20: Kwashiorkor



Fig. 19.21: Flag sign

Acute Complications of PEM

'SHIELDED'—Sugar deficiency (hypoglycemia); Hypothermia; Infections and septic shock; Electrolyte imbalance (hypokalemia, hypomagnesemia), Dehydration, Deficiency of Iron, vitamins and micronutrients.

Age Independent Indices to Diagnose Undernutrition

- Kanawati and McLaren Index: MUAC/Head circumference (cm)
- Rao and Singh index
- Dugdale index
- Quaker arm circumference measuring stick
- Jelliffe ratio (head circumference/chest circumference)

Evaluation of Malnutrition

- **MUAC** (Mid Upper Arm Circumference):
 - Normal value between 1 and 5 years is 16 to 17 cm
 - Value < 13.5 cm is abnormal and suggestive of malnutrition
 - Value < 11.5 cm indicates *severe malnutrition*
- **Shakir tape** method: This special tape has three colored zones—**red, yellow and green** corresponding to < 12.5 cm (*wasted*); 12.5 to 13.5 cm (borderline) and > 13.5 cm (normal) MUAC respectively.
- **Bangle test**: Bangle of **internal diameter 4 cm** is passed above the elbow; in normal children it does not pass above elbow; but in severe malnutrition it does!
- **Skinfold thickness**: Indicates subcutaneous fat; **triceps skinfold** is measured; > 10 mm in normal children; < 6 mm in severely malnourished children.



Fig. 19.22: Shakir tape

Management of Severe Malnutrition—10 Steps

1. Prevent hypoglycemia (**1 Step**). Use **10%** glucose/dextrose.
2. Prevent hypothermia.
3. Prevent dehydration.
4. Correct electrolyte imbalance.
5. Prevent infection.
6. Correct micro-nutrient deficiency.
7. Initiate feeding with caution.
8. Achieve catch up growth.
9. Provide sensory stimulation and emotional support.
10. Prepare for discharge and followup after recovery.

Treatment

- **I stage**: Dehydration and infections are treated during first **24–48 hours**.
- **II stage**: During next **7–10 days**, patients is given a diet of **75 cal/kg/day** with **F-75** (formula 75 diet) along with antibiotics to maintain protein and energy need.
- **III stage**: Providing diet of **175–200 kcal/kg/day** in severe malnutrition.

Obesity in Children

- In children < 2 years, weight for length greater than the 95th percentile indicates overweight
- In children > 2 years
 - BMI > 85th percentile = overweight
 - BMI > 95th percentile = obesity
 - BMI > 99th percentile = severe obesity
- Also Know; underweight status = BMI ≤ 5th percentile for age.

Assessment and Treatment of Dehydration

Condition	Well alert	Restless, Irritable	Lethargic or unconscious, floppy
Eyes	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth and tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly or not able to drink
Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly
Decide	Patient has NO signs of dehydration	If the patient has 2 or more signs, there is SOME dehydration	If the patient has 2 or more signs, there is SEVERE dehydration
Treat	Use treatment plan A	Weight the patient and Use treatment plan B	Weight the patient and use treatment plan C urgently

DEHYDRATION AND REHYDRATION

Maintenance Fluid Requirement in Healthy Children

Body weight	Per day	Per hour
0–10 kg	100 mL/kg	4 mL/kg
10–20 kg	1000 mL for first 10 kg + 50 mL/kg for each kg beyond 10 kg	40 mL + 2 mL/kg for each kg beyond 10 kg
> 20 kg	1500 mL + 20 mL/kg for each kg beyond 20 kg	60 mL + 1 mL/kg for each kg beyond 20 kg

WHO Low Osmolarity ORS (Oral Rehydration Solution)

Osmole or Ion	mmol/L	Constituent	g/L
Sodium	75	Sodium chloride	2.6
Potassium	20	Potassium chloride	1.5
Chloride	65		
Citrate	10	Trisodium citrate, dehydrate	2.9
Glucose	75	Glucose, anhydrous	13.5
Total osmolality	245		

Weight loss in Dehydration

Degree	Loss of body weight
Mild dehydration	3–5% (infant) 3% (older child)
Moderate dehydration	6–10% 6% (older child)
Severe dehydration	11–15% 9% (older child)

Treatment plan A	Treatment plan B	Treatment plan C									
NO dehydration	SOME dehydration	SEVERE dehydration									
<ul style="list-style-type: none"> Mothers educated to use increased amounts of home available fluids Breastfeeding should be continued ORS packets to be used at home 	<ul style="list-style-type: none"> Rehydration therapy: 75 mL/kg ORS in first 4 hours. Maintenance therapy: Begin when signs of dehydration disappear usually within 4 hours—10 mL/kg/stool 	Start IV fluids - Ringer lactate + 5% dextrose or normal saline 100 mL/kg is given IV as shown below <table border="1"> <thead> <tr> <th>Age</th><th>First</th><th>Then</th></tr> </thead> <tbody> <tr> <td>< 12 mths</td><td>30 mL/kg in 1 hour</td><td>70 mL/kg in 5 hours</td></tr> <tr> <td>> 12 mths</td><td>30 mL/kg in 30 mins</td><td>70 mL/kg in 2.5 hours</td></tr> </tbody> </table>	Age	First	Then	< 12 mths	30 mL/kg in 1 hour	70 mL/kg in 5 hours	> 12 mths	30 mL/kg in 30 mins	70 mL/kg in 2.5 hours
Age	First	Then									
< 12 mths	30 mL/kg in 1 hour	70 mL/kg in 5 hours									
> 12 mths	30 mL/kg in 30 mins	70 mL/kg in 2.5 hours									

RESUSCITATION OF NEWBORN

- The aim of neonatal resuscitation is to maintain adequate oxygenation and perfusion of blood throughout the body while steps are taken to stabilize the child and establish long-term hemostasis.
- The **MC indication** for neonatal resuscitation is **asphyxia**. Second MC indication is extreme prematurity.
- The components of neonatal resuscitation are **TABC**:
 - T**—Maintenance of temperature (**between 36.5 and 37.5 °C**): By radiant warmers, drying the baby and removal of wet linen; plastic wrap with a cap, thermal mattress, warmed humidified gases, and increased room temperature plus cap plus thermal mattress. (Note that the ideal temperature of newborn resuscitation room should be **26°–28°C (79°–82°F)**)
 - A**—airway: Establishment of open airway by placing the neonate on his back with slight extension of neck elevating the shoulder $\frac{3}{4}$ or 1 inch of the mattress with the help of rolled blanket or towel. Suction of mouth and nose is done.
 - B**—initiate breathing: tactile stimulation is given and when necessary, bag and mask ventilation is given or ET tube can be used.
 - C**—maintain circulation: This is done by chest compression and/or medications.

Resuscitation Protocol

As soon as the baby is delivered, assess following five signs:

- Term gestation (delivery between 37 and 42 weeks of pregnancy)
 - Good muscle tone (flexed posture and active movement of baby)
 - Active breathing or crying
 - Pink color (look at tongue and lips)
 - Clearance of meconium
- If all signs are positive, NO active resuscitation is required.
 - If any of the 5 signs is absent, baby **requires** resuscitation
 - The baby should be placed under the heat source (radiant warmer) and subjected to a set of intervention known as initial steps.

Initial Steps of Resuscitation

- Positioning**
 - The neonate should be placed on her back or side with the neck slightly extended. This can be achieved by putting a rolled blanket or towel under the shoulders, elevating them $\frac{3}{4}$ or 1 inch off the mattress.
- Suctioning**
 - The mouth and nose should be suctioned. The **mouth is suctioned first** to ensure that there is nothing for the infant to aspirate when the nose is suctioned.
 - One should not insert the catheter very deep in mouth or nose for suction – stimulation of posterior pharynx during the first few minutes after birth can produce a vagal response, causing severe bradycardia or apnea.
 - Therefore, during oral suctioning, a suction tube is gently introduced into the baby's **mouth until the 5 cm mark is at the baby's lip**. During nasal suctioning, a suction tube is introduced up to **3 cm mark into each nostril**.
- Dry, stimulate and reposition**
 - After suctioning, the baby should be dried by using pre-warmed linen to prevent heat loss.
 - A brief tactile stimulation in the form of flicking the soles or rubbing the back may be provided in case of non-establishment of good respiratory efforts.
- Free flow oxygen**
 - If the baby continues to be depressed, provide free flow of oxygen using a facemask.

Vigorous and Non-vigorous Newborn

- Vigorous newborn:** A newborn is classified as **vigorous**, if he has all the three signs are present:
 - Strong respiratory effort
 - Good muscle tone
 - Heart rate greater than 100
- Non-vigorous newborn:** If any of the above 3 signs is present, the newborn is classified as non-vigorous.



Fig. 19.23: Self inflating bag and mask

More one-liners

- For children, **uncuffed and straight blade endotracheal tube** is used.
- Incubation used for thermal regulation of premature neonates are **convection warmed incubators**.
- In case of birth asphyxia, corticosteroids are not used.
- Bag and mask ventilation is **contraindicated** in *Diaphragmatic hernia, trachea-esophageal fistula, and meconium aspiration syndrome*.
- Dose of epinephrine/adrenaline** in neonatal resuscitation: **0–1 to 0–3 mg/kg diluted 1:10,000**.
- Ideal route for administration of drugs in newborn resuscitation is by **umbilical vein catheterization**.

Other Important Points in Neonatal Resuscitation Protocol 2015

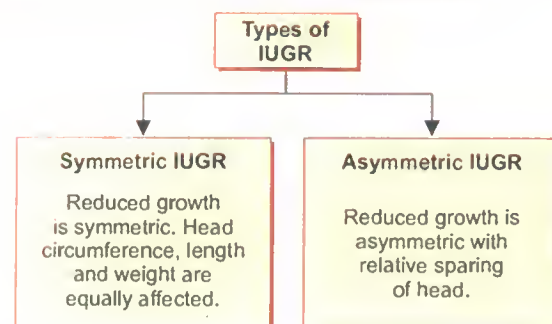
- The new **order** of the assessment questions is (1) Term gestation? (2) Good tone? and (3) Breathing or crying?
- The **Golden minute** (60 seconds) for completing initial assessment and beginning ventilation if required is the same.
- Delayed cord clamping** for more than 30 seconds is reasonable for both term and preterm infants who do NOT require resuscitation at birth.
- Assessment of heart rate during the first minute of resuscitation and use of a **3-lead ECG** may be reasonable.
- Resuscitation of preterm newborns (< 35 weeks gestation) should be initiated with low oxygen concentration of **21–30%**.
- Routine intubation and suctioning even for non-vigorous newborns born through meconium stained amniotic fluid is NOT recommended now.
- 3:1 compression to ventilation ratio** remains unchanged (90 compressions and 30 breaths per minute remains unchanged).

LOW BIRTH WEIGHT

- Birth weight is the single most important determinant of chances of survival, growth and development of an infant. Birth weight should ideally be measured within 1st hour of birth.
- Average birth weight in India is 2.7 to 2.9 kg (2.8 kg).
- MC causes of low birth weight (LBW) in India is maternal malnutrition. Maternal nutrition has linear relation with birth weight.
- Definitions:**
 - Low birth weight (LBW):** Any neonate weighing < 2500 g (2.5 kg) at birth irrespective of gestational age (WHO definition).
 - Very low birth weight (VLBW):** Any neonate weighing less than 1500 g (1.5 kg) at birth irrespective of gestational age.
 - Extremely low birth weight:** Any neonate weighing less than 1000 g (1 kg) at birth irrespective of gestational age.
 - Appropriate for gestational age (appropriate for date): Neonate with birth weight between 10th to 90th percentile.
 - Small for gestational age (small for date) OR intrauterine growth retardation (IUGR):** Neonate with birth weight less than 10th percentile.
 - Large for gestational age (large for date):** Neonate with birth weight more than 90th percentile.
 - Term neonate** (term baby): Neonate born between 37 and <42 weeks (259–293 days), irrespective of birth weight.
 - Preterm baby:** Neonate born before 37 weeks (<259 days), irrespective of birth weight.
 - Post-term baby:** Neonate born at or after 42 weeks (≥ 294 days), irrespective of birth weight.

Causes of IUGR (Small-for-Date)

- Maternal malnutrition: Most important cause.
- Substance/drug intake: Smoking and tobacco, alcohol, propranolol
- Maternal factors: Short stature mother, primi or grand multipara, young mother (< 20 years), low pre-pregnancy weight.
- Maternal illness/diseases: Anemia, CRF, heart disease, malaria, pre-eclampsia, hypertension.
- Placental factor: Abruption placenta, excessive infarct, single umbilical artery.
- Fetal factors: First born babies, genetic/chromosomal aberrations, twin/multiple pregnancies, intrauterine infection.



Ponderal Index

- Ponderal index is used as a indicator of fetal growth status, especially to assess asymmetrical IUGR.
- Ponderal index** = $\text{Weight (g)} \times 100 / \text{length (cm)}^3$.
Ex: for a baby weighing 2000 grams and height of 50 cm, Ponderal index = $2000 \times 100 / (50)^3 = 200000 / 125000 = 1.6$.
- A Ponderal index below the 10th percentile may be used to identify IUGR infants correctly.

Problems of Small for Date Infants (IUGR)

- Birth asphyxia
- Meconium aspiration syndrome
- Hypothermia
- Head circumference is ≥ 3 cm more than chest circumference
- Internal organs like liver, thymus and lungs are shrunken
- Hypoglycemia
- Infections
- Polycythemia and hyperviscosity
- Hypocalcemia.

PREMATURITY

Features of Prematurity

- Baby is small in size usually less than 47 cm long.
- Head is relatively large, sutures are widely separated and fontanelle are large.
- Face is small and buccal pad of fat is minimal.
- Skin is thin and pinkish and appears shiny due to generalized edema.
- Skin is covered with abundant lanugo and there is little vernix caseosa.
- Subcutaneous fat is reduced.
- The breast nodule is less than 5 mm wide.
- The ears are soft and flat with ear cartilage being deficient and pliant

- Testes are not descended into scrotal sac (empty scrotum).
- Scrotal sac is poorly pigmented and has less rugosity.
- In females, labia majora appears widely separated, exposing the labia minora and the clitoris.
- Deep creases are not well developed in the sole.
- There may be a single deep crease over the anterior one third of the sole.
- Neonatal reflexes, such as moro, suckling and swallowing are sluggish.
- There is hypotonia with a poor recoil of flexed forearm when extended.
- The liver of premature (preterm) neonate is functionally immature that leads to hypoglycemia, hyperbilirubinemia and poor detoxification of drugs.

Complications of Prematurity (Preterm Baby)

- Birth asphyxia; Hypothermia; Feeding difficulties; Infections; Respiratory distress; ARDS (Hyaline membrane disease); Apnea; Intraventricular hemorrhage; (MC in subependymal germinal matrix). Necrotizing enterocolitis; Metabolic acidosis; Hyperbilirubinemia; Hypoglycemia; Hypocalcemia; Hypoproteinemia

Feeding of Preterm (Premature) Neonate

Gestational age	Initial feeding method
<28 weeks	Intravenous fluids
28–31 weeks	Orogastric (or nasogastric) tube feeding with occasional spoon/paladal feeding
32–34 weeks	Feeding by spoon/cup Orogastric tube feeding if spoon feeding is not possible
>34 weeks	Breastfeeding

MORE ONE-LINERS

- Brown adipose tissue** is mainly found around the kidneys, adrenal glands, between the scapulae, in axilla, along the spinal column and around the blood vessels of the neck, mediastinum and loin. **Subcutaneous fat is white.** In infants **brown adipose tissue** contains a protein called **thermogenin** which releases heat.
- Encopresis** refers to the passage of feces into inappropriate places after a chronological age of 4 years (or equivalent developmental level).
- Causes of Floppy Infant:** Down's syn; Prader-Willi syn; Werdnig Hoffmann disease; Central core disease; Nemaline myopathy; Ehlers-Danlos syn; Polymyositis; Glycogen storage disease; Hypercalcemia; Botulism.

- MC indication for liver transplantation in children is extrahepatic biliary atresia** after a failed portoenterostomy (**Kasai procedure**).
- MC indication for heart transplants in infants is congenital heart disease (hypoplastic left heart syndrome MC)** whereas in **older children and adolescents it is cardiomyopathy**.
- McEwan's sign:** Percussion of the skull near the junction of frontal, temporal and parietal bones will produce a stronger resonant sound (**cracked pot sound**) when either **hydrocephalus or brain abscess** is present (in child).
- Normal **serum retinol levels** in **newborn** is 20–50 microg/dL.

- Color of **transition stools** is **yellow**.
- The **anterior fontanel** close by **18 months of age**.
- Posterior fontanel** are fused by **3 months of age**.
- Morphine** is NOT used in children due to **persistent respiratory depression**.
- Probiotics may be helpful to prevent traveler's diarrhea.
- Zinc supplementation can decrease diarrhea related morbidity and mortality.

TERATOGENIC DRUGS

- Teratogenic drugs = drugs taken during pregnancy with adverse effects on the neonate.

Drug	Adverse effects
Anticonvulsants	
Phenytoin	Fetal hydantoin syndrome (microcephaly, cleft palate, hypoplastic changes, IUGR)
Carbamazepine	Spina bifida
Phenobarbitone	Relatively safe
Sodium valproate	Neural tube defect (NTD) , hypospadias , microstomia, developmental delay
Hormonal agents	
Corticosteroids	Growth retardation, cleft palate and lip
Diethyl stilbestrol	(Used as 'morning-after' pill) Vaginal adenosis in female offspring in adolescence Clear cell vaginal adenocarcinoma in teenagers In male offspring (risk of testicular cancer in later life)
Antithyroid drugs	
Clomiphene	NTD, multiple gestation , Down's syndrome
Synthetic progestins	Masculinization in female fetus, hypospadias
Antibiotics	
Chloramphenicol	'Gray baby syndrome' (peripheral vascular collapses)
Sulphonamides	Kernicterus, methemoglobinemia
Tetracyclines	Dental discoloration (yellow) and deformity. Inhibition of bony growth, cataracts
Aminoglycosides	Fetal ototoxicity due to eighth N. damage
Antimalarials	Intrauterine death
Quinine, chloroquine	Retinopathy, congenital deafness, corneal opacities
Psychiatric drugs and substances of abuse	
Lithium	Ebstein's anomaly (downward displacement of an abnormal tricuspid valve into the right ventricle)
LSD (lysergic acid diethylamide)	'Fractured chromosomes' anomaly in fetus, stunted growth
Heroin	Irritability, hyperactivity, tremors
Cocaine	Abruptio placentae, preterm labor, cerebral infarction
Beta-blockers	Fetal bradycardia
Amphetamines	Hepatic calcification ; generalized arteritis, learning disability, motor incoordination

Contd...

Cont'd

Drug	Adverse effects
Anticoagulants	
Vitamin K (large dose)	Hyperbilirubinemia (hemolysis) and kernicterus
Disumarol	Intrauterine death, severe bleeding in neonate
Warfarin	Conradi's syndrome: skeletal and facial anomalies, chondrodysplasia punctata, hemorrhage
Aspirin	Hemorrhagic disease of newborn
Other drugs	
Cytotoxic drugs	Multiple fetal malformations and abortion
Isotretinoin	CNS defects, facial palsy, deafness, cardiac defects (<i>accutane embryopathy</i>)
Oxygen in high concentrations	Retrolental fibroplasia and blindness
Thalidomide	Phocomelia (seal limbs), cardiac malformations (was historically used as a <i>sedative</i>); Absence/shortening of long bones
Thiazide diuretics	<i>Neonatal thrombocytopenia</i>
ACE Inhibitors	Renal tubular dysgenesis, lung hypoplasia, anuria, oligohydramnios
Misoprostol (prostaglandin)	Mobius syndrome , arthrogryposis
Vitamin D	Williams syndrome (infantile hypercalcemia, <i>supravalvular aortic stenosis</i> , elfin facies)
Alcohol	Fetal alcohol syndrome: Prenatal-onset growth deficiency, developmental delay, facial dysmorphism (short palpebral fissures, ptosis, strabismus, ear abnormality, long philtrum with a thin upper lip, small teeth with faulty enamel), aberrant palmar crease, multiple joint anomalies and cardiac defects (ASD > VSD); ADHD ; low IQ, microcephaly, increased breech presentations
Heroin	Irritability, hyperactivity, tremors
Cocaine	Abruptio placentae, preterm labor, cerebral infarction
Beta-blockers	Fetal <i>bradycardia</i>
Amphetamines	Hepatic calcification ; generalized arteritis, learning disability, motor incoordination
Anticoagulants	
Vitamin K (large dose)	Hyperbilirubinemia (hemolysis) and kernicterus
Disumarol	Intrauterine death, severe bleeding in neonate
Warfarin	Conradi's syndrome: skeletal and facial anomalies, chondrodysplasia punctata, hemorrhage
Aspirin	Hemorrhagic disease of newborn
Other drugs	
Cytotoxic drugs	Multiple fetal malformations and abortion
Isotretinoin	CNS defects, facial palsy, deafness, cardiac defects (<i>accutane embryopathy</i>)
Oxygen in high concentrations	Retrolental fibroplasia and blindness
Thalidomide	Phocomelia (seal limbs), cardiac malformations (was historically used as a <i>sedative</i>); Absence/shortening of long bones
Thiazide diuretics	<i>Neonatal thrombocytopenia</i>
ACE Inhibitors	Renal tubular dysgenesis, lung hypoplasia, anuria, oligohydramnios
Misoprostol (prostaglandin)	Mobius syndrome , arthrogryposis
Vitamin D	Williams syndrome (infantile hypercalcemia, <i>supravalvular aortic stenosis</i> , elfin facies)

Drugs Taken During Perinatal/Neonatal Period and their Effects on the Neonate

Medications to mother	
• Oxytocin	Hyperbilirubinemia
• Prolonged cortisone	Adrenal crisis in infants
• NSAIDs	Premature closure of ductus arteriosus
• Dexamethasone	Periventricular leukomalacia
Medications to baby	
• Chloramphenicol	Grey baby syndrome
• Erythromycin	Pyloric stenosis
• Vitamin K	Bleeding, hepatotoxicity



Fig. 19.24: Phocomelia

FDA Categories for Drug Use in Pregnancy

Category		Examples
A	No risk to fetus as demonstrated in human studies (in pregnant women in first trimester)—safest drug	Folic acid, levothyroxine,
B	No risk to fetus as demonstrated in animal studies BUT no controlled studies in pregnant women OR Animal studies have shown adverse effect BUT controlled studies in pregnant women have failed to demonstrate risk to the fetus	Penicillin, cephalosporins, erythromycin,
C	Animal studies indicate a fetal risk BUT no controlled studies in pregnant women OR No animal studies have been conducted and no controlled studies in pregnant women	Glucocorticoids
D	Positive evidence of fetal risk exists, but benefits may outweigh the potential risk	Antiepileptics
X	Definite fetal risk based on human or animal studies and the risk clearly outweighs any benefit (i.e. the drug is absolutely contraindicated)	Quinine, warfarin, isotretinoin

Orthopedics

HISTORY OF ORTHOPEDICS

- **Nicholas Andry** coined the word 'orthopedics' derive from the Greek words 'orthos'—correct and 'paidion'—child—when he published 'orthopedie' (French)—translated as orthopedia—the art of *correcting and preventing deformities* in children (1741).

- **Sir John Charnley** is the father of hip replacement surgery (arthroplasty).
- **Thomas' splint**—designed by **Hugh Owen Thomas** for *treating TB knee* patients, but later widely used for femoral fractures; it provides *continuous fixed traction*.

'NAMED' FRACTURES

Vertebral fractures

Jefferson's #	Burst # of the Atlas (C1); ('Jeffers1=C1')
Hangman's #	Traumatic spondylolisthesis of C2, # of pedicles and pars interarticularis of C2
Clay shoveller's #	# of spinous process of T1 vertebra; ('1 T-pot made of clay!') {Lower cervical and upper thoracic vertebrae, C6, C7, T1}
Chance #	Horizontal # through vertebra (body, pedicles, laminae) due to sudden deceleration with lap-only seatbelt; usually L1 or L2

Upper limb fractures

Little leaguers elbow	Avulsion # of the medial epicondyle of humerus
Piedmont #	Closed # of radius at the junction of the middle and distal thirds' no associated ulnar fracture
Barton's # (Marginal #)	Intra-articular # of distal articular surface of radius
Chauffeur's #	# of radius just above the styloid process caused by backward jerk of the starting handle of a car, in olden days
Colles' #	# occurring in adults at the corticocalcaneal junction of the distal end of radius with dorsal tilt and other displacements.
Smith's #	Reverse of Colles' #
Galeazzi #	# of distal third of Radius with dislocation of distal radioulnar joint. (aka <i>reverse Monteggia fracture</i>)
Monteggia's #	# of proximal third of Ulna with dislocation of head of radius 'MURG = Monteggia # Ulna, Radius # Galeazzi'
Hume's #	High Monteggia # commonly in children
Moore's #	# of distal end of radius with luxation of distal end of ulna
Bennett's # dislocation	Oblique intra-articular # of base of first metacarpal with subluxation of trapeziometacarpal joint
Rolando's #	Old intra-articular # across the base of the first metacarpal
Boxer's #	Ventrally displaced # through neck of fifth metacarpal
Essex-Lopresti #	Comminuted # of radial head with distal radio-ulnar joint subluxation; there is rupture of interosseous membrane with instability of forearm

Contd...

Contd...

Lower limb fractures

Unsolwed #	Intracapsular fracture neck of femur
Segond's #	a/w ACL tear of the knee
Stieda's #	# of medial condyle of femur; a bony outgrowth from that region is called Pelligrini's disease
Masonniase's #	Ankle injury with # of neck of fibula
Pilon #	Comminuted # of tibial articular surface with # of Fibula
Bumper #	Comminuted depressed # of lateral tibial condyle
Gosselin's #	V Shaped # of distal end of tibia
Tillaux #	Salter type 3 # of the lateral part of the distal tibial epiphysis
Toddler's #	A nondisplaced spiral # of tibia
Cotton's #	Trimalleolar ankle # (MC due to supination external rotation injury - MC mechanism of ankle fracture)
Pott's #	Bimalleolar ankle #
Wagstaffe's #	# with displacement of medial malleolus
Aviator #	# of neck of talus, occurs in aircraft crash where the rudder bar is driven forcibly against the middle of the sole of foot resulting in forced dorsiflexion of ankle
March #	Stress # of shaft of second or third metatarsal; occurs in fresh army recruits who march for long time; <i>heals spontaneously</i>
Jone's #	Avulsion # of base of fifth metatarsal

Miscellaneous fractures

Buttonhole #	# with loss of bone as in gunshot wound
Cough #	Rib (fifth or seventh) # caused by coughing
Dyscrasic #	# occurring in general malnutrition
Sprain #	# in which a ligament, capsule or tendon tears off a portion of bone
Greenstick #	Hickory stick or Willow #. Bending of a bone with incomplete # involving convex side of the bone only (only cortex is fractured)
Pond #	Depressed skull # in infants
Shepherds #	# of external tubercle (posterior process) of talus, sometimes mistaken for a displacement of os trigonum
Ping pong #	Depressed skull #, also called dishpan # or derby hat #
Tripod #	Trimalar #, involving the inferior orbital rim, lateral orbital wall and fracture/dislocation of zygomatic arch
LeFort #	Fractures of maxilla LeFort 1 = Guerin's # LeFort 2 = Pyramidal # LeFort 3 = Craniofacial disjunction
Motorcyclists #	Fracture of <i>base of skull</i> into anterior and posterior halves
Malgaigne #	Vertical shear fracture of pelvis
Dyscrasic #	# due to malnutrition



Fig. 20.1: March fracture' at the neck of 2nd metatarsal. Note the healing response by formation of abundant callus

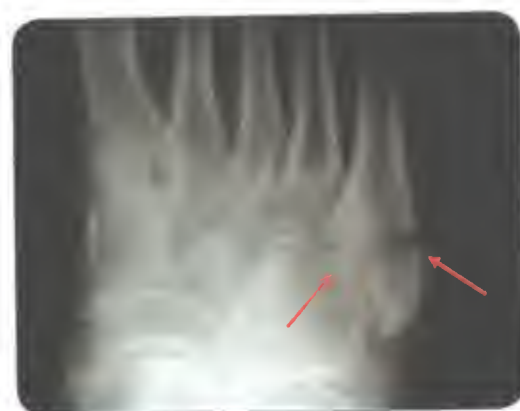


Fig. 20.2: Radiograph of a Jones' fracture

BASICS

Stages of Fracture Healing

1. Hematoma formation
2. Inflammation
3. Callus formation
4. Consolidation
5. Remodeling

Bone Markers

Bone formation markers	Bone resorption markers
<ul style="list-style-type: none"> Serum total alkaline phosphatase Serum bone-specific alkaline phosphatase Serum osteocalcin Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP 	<ul style="list-style-type: none"> Urinary hydroxyproline Urinary total pyridinoline (PYD) Urinary free deoxypyridinoline (DPD) Urinary collagen type 1 cross-linked N-telopeptide (NTX) Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX) Bone sialoprotein (BSP) Tartrate-resistant acid phosphatase

Immature (Growing) Skeleton

- Growing bone is **less brittle** and **more malleable** than mature bone due to fewer lamellar components and greater.
- The **periosteum enveloping growing bones is stronger and thicker** than mature periosteum.
- The immature periosteum possesses **increased osteogenic capability**, and **new subperiosteal bone is rapidly laid down**.
- Non-union is rare** in children's fractures.
- Plane of deformity with respect to adjacent joint: **remodeling occurs more readily in the plane of a joint** than with deformity not in the plane of the joint; also remodelling is better when fracture occurs close to the physis (i.e. the closer a fracture is to the growing end, the faster it remodels!).
- Stiffness and contractures are less of a problem in children's fractures; angular deformity easily gets corrected by remodeling.
- Incomplete fractures in children** include:
 - Greenstick fracture
 - Buckle (torus) fracture
 - Plastic (bowing) fracture.

Non-Union

- Definition of non-union** (FDA panel): Non-union is said to be established when a minimum of **9 months has elapsed since the injury** and the fracture shows **no signs of healing continuously for 3 months**.
- X-ray features of non-union**
 - Roundening of fracture surfaces
 - Fracture becomes rather sharply defined
 - Cystic changes occur in one or both fragments.

Common sites of non-union

- Neck of femur
- Scaphoid
- Lower third of ulna
- Lower third of tibia
- Lateral condyle of humerus

Avascular Necrosis (Osteonecrosis)

- Risk factors:** Fractures and Trauma, **Alcoholism**, **Cushing's syndrome**, **Corticosteroid** therapy, **Caisson disease**, Connective tissue disorder, Chronic **renal dialysis**, **Diabetes mellitus**, **Gaucher's disease**, **Meta-static malignancy**, Organ transplantation, Pancreatitis, Pregnancy, Rheumatoid arthritis, **Radiotherapy**, **Sickle cell anemia**, SLE.

Common sites of avascular necrosis

- Head of femur (due to # neck of femur, posterior dislocation of hip)
- Proximal pole of scaphoid (due to # waist of scaphoid)
- Body of Talus (due to # neck of talus)

- MRI is the most sensitive** (~95%) modality and demonstrates changes well before plain film changes are visible. The progression is: **diffuse edema**; focal **serpiginous low signal line** with fatty center (MC appearance), **double line sign** on T2WI is diagnostic; osteochondral fragmentation (rim sign); secondary degenerative change.
- Bone scan:** Early stage: **cold spot**; Late stage: cold spot with surrounding high uptake ('**doughnut sign**').
- Ficat classification** is a commonly used system to **stage AVN of the hip**, and uses a combination on plain film, MRI and clinical features:

Plaster Casts and Their Use

Name of cast	Use
Frog-leg or Lorenzo cast, Bachelor's cast	Congenital dislocation of hip
Minerva cast	Cervical spine disease
Reissers, Turn buckle cast, Milwaukee brace	Scoliosis
Shoulder spica	# Around shoulder
Hip spica	# Femur
U Slab, Hanging Cast	# Humerus
Colles' cast	Colles' #
Cylinder cast	# Patella
Patellar tendon bearing cast	# Tibia

EXTRA EDGE

- Lorenzo's oil:** Used in adrenoleukodystrophy (asked in previous NEET).

Splints

Name	Use
Thomas splint, Bohler Braun splint	# Femur
Aluminium splint	Immobilization of fingers
Dennis Brown splint	CTEV
Shoulder abduction splint	Axillary nerve (deltoid paralysis)

Contd...

Contd...

Name	Use
Knuckle bender splint	Ulnar N palsy (lumbricals paralysis)
Foot drop splint	Sciatic N palsy or common peroneal N palsy
Von-Rosen splint, Craig Splint	Cong Dysplasia Hip
Cockup splint	Radial N palsy (extensors of wrist and MP joints paralysed)
Aeroplane splint	Brachial plexus injury

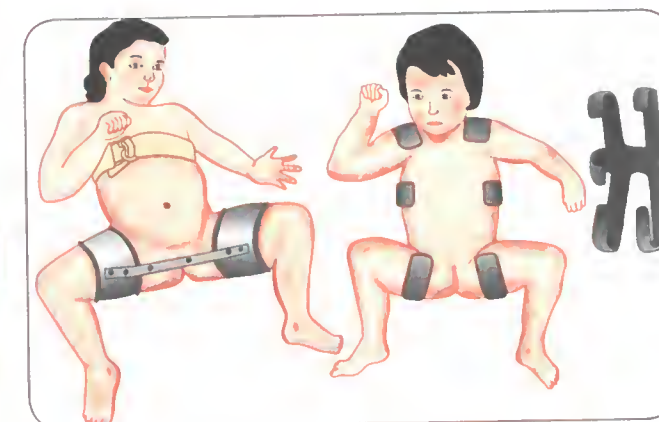
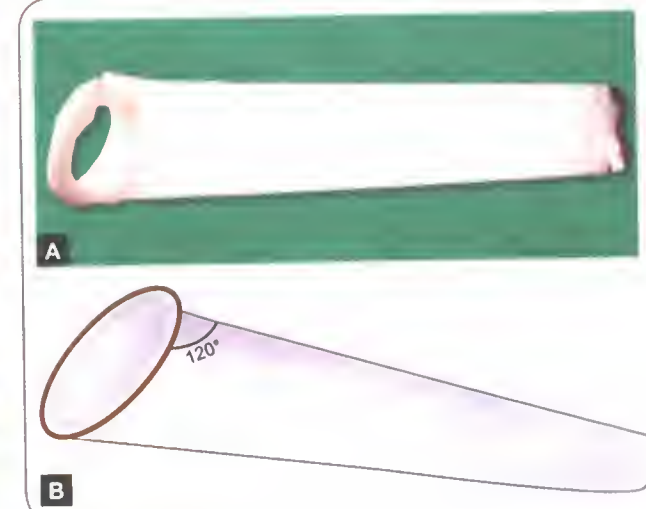


Fig. 20.3: Craig splint and von Rosen splint



Figs. 20.4A and B: Thomas' splint. Note the convergence of the side bars, placement of the ring which is at 120° to the inner bar and for universal use, the bars are welded to the ring in the middle bisecting it into two equal halves

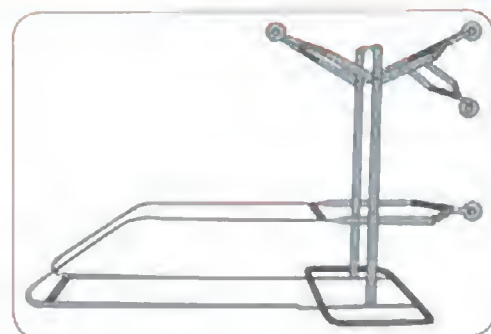


Fig. 20.5: Bohler-Braun splint

Tractions

Tractions	Indications
Gallows traction, Bryant's 90-90 traction	# Shaft femur in children <2 yrs
Perkin's traction	# Shaft of femur in adults
Russell's traction	Trochanteric fracture
Buck's traction	Conventional skin traction
Dunlop's, Smith's traction	Supracondylar # humerus
Agnes Hunt traction	For fixed flexion deformity of hip
Well leg traction	For correction of adduction/abduction deformity of hip
Halo-pelvic traction	Spinal injury (thoracic and lumbar spine)
Head halter traction; Crutchfield traction	Cervical spine injuries

- **Skin tractions** are: Dunlop's, Buck's Russell's; Bryant's, Cottrell's
- In **skeletal traction**, upto 20 kg weight is permitted.
- In **skin traction** 5-7 kg weight is permitted.
- Pins used for skeletal traction: **Steinmann pin**/Bohler pin (smooth pin) and **Denham's pin** (threaded pin); also **K wires** are used.



Fig. 20.6: Bryant's traction/Gallows traction



Fig. 20.7: Crutchfield tongs used for skull traction

Fixations Systems

- **Ilizarov technique** is based on theory of **distraction histogenesis**.
- Examples of **external fixators** are: Ilizarov system, Hoffman system; rail system, Schanz pins, Joshi's pins.
- Examples of **internal fixators**: Plates and screws (dynamic and locking compression plates); Kirschner wires (K-wires) and Intramedullary (I-M) nails. Knowle's pin was used in percutaneous fixation of # neck of femur.

Few Named Osteotomies

Osteotomy	Indication
McMurray's	# neck of femur
Pauwel's	Osteoarthritis hip; # neck of femur
High tibial	OA knee
French	Correction of gunstock deformity
Spinal	Ankylosing spondylitis
Salter's, Chlari's, Pemberton's	Acetabular reconstruction (used in CDH)

Arthrodesis

- Arthrodesis is the fusion of joints by surgical methods; since it limits the functions of the joint, arthroplasty is used nowadays; however, arthrodesis, when performed—each joint should be fixed in its functional position to allow the patient to still continue using it.

Joint	Optimal position of arthrodesis
Knee	10-15 deg flexion
Hip	10-30 deg flexion, no abduction, adduction or rotation
Ankle	At right angle

Contd...

Contd.

Joint	Optimal position of arthrodesis
Wrist	10-20 deg dorsiflexion
Elbow	Right hand 90 deg flexion and left hand 70 deg flexion
Shoulder	30 deg abduction; forward flexion 40 deg and internal rotation 40 deg

Open Fracture Treatment

Four essentials of management are:

1. Antibiotic prophylaxis
2. Urgent wound and fracture **debridement** (most important)
3. Stabilization of fracture
4. Early definitive wound cover

INJURY

Mechanisms of Injury

Mechanism	Injury
Fall on outstretched hand	# Clavicle; # around elbow
Dashboard injury	Posterior hip dislocation
Fall onto heel	# Calcaneum
Hit by stick to forearm	# Ulna
Slip in bathroom (trivial trauma)	# Neck of femur

Characteristic Deformities by Injuries

Deformity	Injury
Flattening of shoulder	Shoulder dislocation (anterior)
Cubitus varus (Gunstock deformity)	Supracondylar # humerus
Cubitus valgus and Tardy Ulnar nerve palsy	# Lateral condyle humerus
Dinner Fork (Velpeau's)	Colles #

Type	Wound	Level of Contamination	Soft tissue Injury	Bony Injury
I	< 1 cm long	Clean	Minimal	Simple, minimal comminution
II	> 1 cm long	Moderate	Moderate, some tissue damage	Moderate comminution
IIIA	Usually < 10 cm long	High	Severe, with crushing	Usually comminuted; soft tissue coverage of bone possible
IIIB	Usually > 10 cm long	High	Very severe loss of coverage; usually requires soft tissue reconstructive surgery	Moderate to severe comminution with periosteal stripping
IIIC	Usually > 10 cm long	High	Very severe loss of skin coverage + vascular injury requiring repair; may require soft tissue reconstructive surgery	Bone coverage poor ; maybe moderate to severe comminution

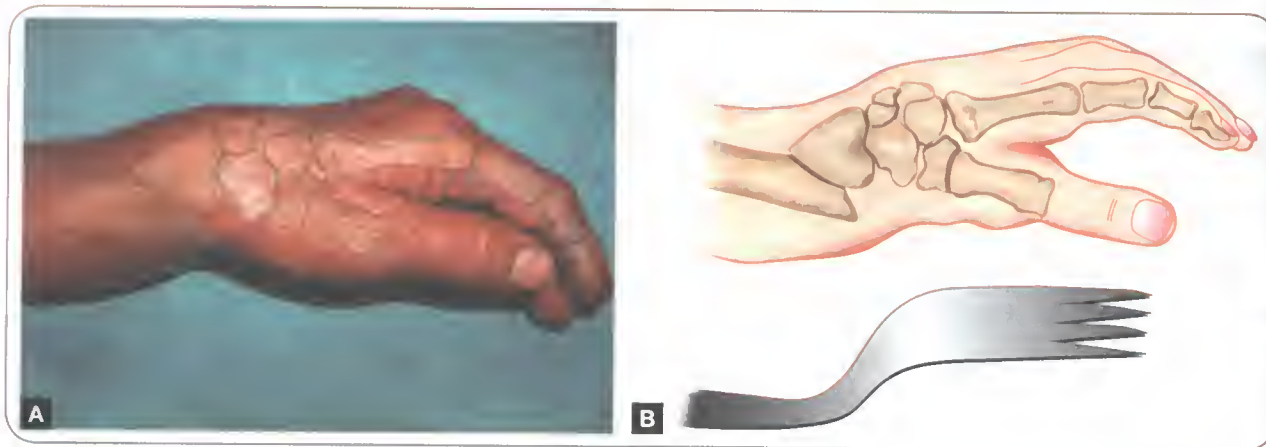
Deformity	Injury
Garden spade (opposite of dinner fork)	Smith's fracture
Abduction, External rotation	Anterior hip dislocation
Flexion, AD duction, I nternal Rotation	Posterior hip dislocation 'Papa! (Father!) = FADIR '
Coxa Vara	Trochanteric #
Genu valgum	Condylar # of tibia
External rotation of leg	# Neck of femur; Trochanteric #
Mallet finger	Avulsion of insertion of extensor tendon from distal phalanx; treat with splint with joint in extension for 8 weeks
Jersey finger (Rugby finger or Sweater finger)	Avulsion of the flexor digitorum profundus (FDP) at the base of the distal interphalangeal joint
Gamekeeper's thumb	Ulnar collateral ligament injury
Winging of Scapula	Injury to long thoracic Nerve of Bell (N. to serratus anterior)

Dislocations at Different Joints

Joint	MC dislocation
Knee, Hip, Elbow (KHELI)	Posterior MC
Spine	Cervical spine (anterior C5 over C6)
Shoulder	Anterior MC
Patella	LA teral MC
Ankle	Antero LA teral MC
Intertarsal	Chopart's dislocation
Tarsometatarsal	Lisfranc's dislocation

Gustilo Anderson Classification

- Gustilo Anderson classification system (1976) is the MC used classification for **open (compound) fractures**.



Figs. 20.8A and B: Classical 'Dinner fork' deformity of a Colles' fracture, clinical picture and diagrammatic representation



Fig. 20.9: The clinical photograph of the deformity



Fig. 20.11: Normal left hand where the thumb is placed at right angles to the other fingers and the right hand with 'Ape thumb' deformity where the thumb is remaining parallel by the side of the other fingers



Fig. 20.10: An avulsion fracture of the base of distal phalanx. The resultant deformity is a 'Mallet finger'. The patient is a goalkeeper and the injury happened during a soccer match when he blocked a penalty kick. Avulsion force is exerted by the lateral slips of the extensor expansion



Fig. 20.12: Positive Ochsner's clasp test and the pointing index sign. Seen only in high median nerve injury



Fig. 20.13: A negative pen test. The person is able to touch the pen using his abductor pollicis brevis. Positive sign (not able to touch the pen) is seen in both high and low median nerve injury

More One Liners

- **Carrying angle** at elbow is 11° in male, 14° in females.
- Causes of **Crepitus** are Fracture; Hematoma; Surgical emphysema; Gas gangrene; OA; Tenosynovitis; Charcot's joint.
- **Snow storm appearance** on chest X-ray is suggestive of **fat embolism**.
- **Stress #** with normal bone (i.e. not osteoporotic)
- Investigation of choice in **stress fracture** - **MRI**.
- Comminuted fractures unite fastest because the greater the fracture surface the faster the union.
- **Bone cement setting time** is 8–10 minutes.
- Bone cement substance commonly used for artificial bone graft - hydroxyapatite.
- **Plaster of Paris** is calcium sulfate hemihydrate ($\text{CaSO}_4 \frac{1}{2} \text{H}_2\text{O}$).
- **Appositional bone growth** refers to increase in thickness or girth of bone.
- The term '**bone bruise**' or 'bone contusion' refers to trabecular microfractures due to impaction of bone - **MRI** is needed to detect this in acute stages.
- **Common sites of tendon rupture** include **supraspinatus, biceps, patella, Achilles, posterior tibial and peroneal**.
- The rate of **newly synthesized osteoid mineralization** is best estimated by **tetracycline labeling**.
- **Spiral #** in children suggests **child abuse**.

Common Nerve Injuries and Effects

Nerve	Trauma and effects
Axillary	Anterior dislocation of shoulder Deltoid paralysis, flat shoulder , ' regimental badge anesthesia '

Contd...

Contd...

Nerve	Trauma and effects
Radial	# Shaft of humerus
Median	Supracondylar # humerus
Ulnar	# Medial epicondyle humerus
Sciatic	Posterior dislocation of hip Foot drop , wasting of gastrocnemius (calf)
Common peroneal	Knee dislocation, # neck of fibula Foot drop (also inability to evert the foot and sensory loss over anterolateral part of leg)

MEDIAN NERVE INJURY

- **Pointing index (Ochsner's clasp test)** - Flexor digitorum superficialis and flexor digitorum profundus of the index finger are paralyzed - **anterior interosseous nerve** injury.
- **Pen test** - tests the *abductor pollicis brevis*
- **Ape thumb** (simian deformity)
- Wasting of thenar muscles

ULNAR NERVE INJURY

- **Ulnar nerve** travels through the **Guyon's canal (pisohamate canal)** at the wrist.
- Ulnar nerve is very **vulnerable to superficial lacerations** on ulnar side of the wrist (such as a glass piece injury of hand).
- The **ulnar nerve** is the **MC injured peripheral nerve during surgery** because of its superficial location at the elbow (due to compression between the patient and the surgical table).
- **Only low ulnar nerve injury** results in **partial claw hand**; (ring and little fingers only/medial two fingers only) - sometimes called '**hand of benediction**' (also seen in proximal median nerve injury)
- **If both ulnar and median nerves are involved** (low ulnar and low median; high ulnar and low median) the deformity of **total or combined claw hand** otherwise called the '**simian hand**' develops.
- Wasting of hypothenar muscles, hollowing between metacarpals (interossei).

Ulnar Paradox

- **High** ulnar nerve palsy = injury proximal to the elbow.
- **Low** ulnar nerve palsy = injury in distal third of forearm (**Flexor Digitorum Profundus spared**).

In **high ulnar nerve lesion**, the flexor carpi ulnaris is paralyzed and there is '**ulnar paradox**', i.e. **higher the injury lesser the deformity** as along with intrinsic muscles, extrinsic muscles are also paralyzed. Medial half of flexor digitorum profundus is also paralyzed resulting in lesser amount of clawing than in lower ulnar nerve palsy.

Signs of Ulnar Nerve Palsy

Sign	Findings
Froment's sign/Book test:	When the adductor pollicis (Ulnar N) is paralyzed patient tries to hold the book by using the flexor pollicis longus (Median N) in place of adductor
Egawa test	Unable to abduct middle finger/fingers against resistance (<i>weak dorsal Interossei</i>)
Card test	Unable to hold card between fingers (<i>weak palmar interossei</i>): 'PAD = <u>P</u> almar <u>A</u> dduct; <u>DAB</u> = <u>D</u> orsals <u>A</u> Bduct'



Fig. 20.14: Card test being performed. Note that both the examiner and the subject to be examined are using the same grip, i.e. Interdigital clasp



Fig. 20.15: Book test being performed and the Froment's sign. Note the flexion of the interphalangeal joint of the thumb (white arrow) which is brought about by the flexor pollicis longus



Fig. 20.16: Egawa's test being performed. Note how the other fingers are stabilized and the middle finger is made to move sideways both medially and laterally, testing both palmar and dorsal interossei

RADIAL NERVE INJURY

Radial nerve is MC injured of the main upper limb nerves. It innervates *Brachioradialis*, *Extensors* of wrist and fingers, *Supinator*, *Triceps (BEST)*; also called '*great extensor nerve*'.

High Radial Nerve Palsy

- Radial nerve Injury in the spiral groove at mid-humerus level. Triceps is spared and elbow extension is intact.
- Supinator and brachioradialis are paralyzed and there is paralysis of wrist extensors - resulting in wrist drop.
- Compression of radial nerve in axilla (*Crutch palsy*) or mid humerus level (*Saturday night palsy*+) causes - neuropathy/paresis of radial nerve.

Low Radial Nerve Palsy (PIN Injury)

- At the level of the radial head, radial nerve divides into a sensory branch and a motor branch - the *posterior interosseous nerve (PIN)* which passes through the supinator - compression at proximal edge of supinator below arcade of Frohse causes posterior interosseous nerve syndrome.
- Leads to *Flnger drop* and *thumb drop*.
- PIN does NOT supply the brachioradialis, supinator, ECRL, ECRB and anconeus which are directly supplied by radial nerve. Hence wrist extension is possible but not the finger and thumb extension.

Treatment of Radial Nerve Palsy

- *Modified Jones transfer* involves transferring tendon of pronator teres to extensor carpi radialis brevis (PT > ECRB).
- Others are *Brand* transfer and *Boyes* transfer.
- Also Know: Jones transfer also is the name for correcting *claw toe deformity*.

Entrapment Neuropathies

Entrapment syndrome		Precipitating activity	Examination
Carpal tunnel syndrome (median nerve trapped in carpal tunnel at wrist)	Numbness, pain or paresthesias in fingers	Sleep or repetitive hand activity	Sensory loss in thumb, second, and third fingers. Weakness in thenar muscles ; Inability to make a circle with thumb and index finger Tinel and Phalen signs
Ulnar nerve entrapment in cubital tunnel at the elbow	Numbness or paresthesias in ulnar aspect of hand	Elbow flexion during sleep; elbow resting on desk	Sensory loss in the little finger and ulnar half of ring finger Weakness of the Interossei and thumb adductor; claw-hand
Ulnar nerve entrapment at the wrist (<i>Guyon's canal</i> ; <i>pisohamate canal</i>)	Numbness or weakness in the ulnar distribution in the hand	Unusual hand activities with tools, bicycling	Like UNE but sensory examination spares dorsum of the hand, and selected hand muscles affected
Radial nerve entrapment at the spiral groove or axilla	Wrist drop	Sleeping on arm after inebriation with alcohol— ' Saturday night palsy '	Wrist drop with sparing of elbow extension (triceps sparing); finger and thumb extensors paralyzed; sensory loss in radial region of wrist
Meralgia paresthetica (lateral femoral cutaneous nerve entrapped below)	Pain or numbness in the anterior lateral thigh	Standing or walking	Sensory loss in the ' pocket of the pant ' distribution
Peroneal nerve Entrapment at the fibular head	Footdrop	Usually an acute compressive episode identifiable; weight loss	Weak dorsiflexion, eversion of the foot
Tarsal tunnel syndrome (<i>posterior tibial nerve</i> in tarsal tunnel)	Pain and paresthesias in the sole of the foot but NOT in the heel	At the end of the day after standing or walking; nocturnal	Sensory loss in the sole of the foot Tinel's sign at tarsal tunnel

TENDON AND FASCIAL DISORDERS

Carpal Tunnel Syndrome

- **Causes:** *Rheumatoid arthritis*; *diabetes*; *pregnancy*; Wrist OA; *Colles' #*; *Myxedema*; *Acromegaly*; Dislocation of lunate bone; cardiac failure, premenstrual, hyperparathyroidism; amyloidosis, sarcoidosis, familial; mucopolysaccharidoses
- Compression of *median N* as it passes beneath the flexor retinaculum
- **Tingling and numbness in the radial two and half fingers more prominent during sleep**; In later stages **wasting of thenar eminence** and decreased sensation over lateral 3 and half fingers; lateral palmar sensation is spared.

Provocative tests for carpal tunnel syndrome

- **Phalen's sign:** Holding the wrist hyperflexed for 1-2 mins reproduces the symptoms and symptoms will disappear as soon as the wrist is straightened.
- **Tinel's test:** Tapping over the tunnel to produce parasthesiae.
- '**Phalen's PHL**exing, **Tinel's T**apping!'
- **Durkan's Carpal compression test:** Direct compression over carpal tunnel produces symptoms.
- **Tourniquet test**
- Hand elevation test and reverse Phalen test

Guyon's Tunnel Syndrome (Ulnar Nerve)

Ulnar nerve compression in *Guyon's canal* leading to tingling and numbness in the **ring and little fingers with**

hypothenar wasting; dorsal sensations over the ring and little fingers **are preserved**.

Ganglion

- Smooth multilocular jelly like swellings that are bulges of synovium (e.g. on dorsum of **wrist MC**)
- They communicate with joint capsules or tendon sheaths; asymptomatic and treatment usually NOT needed
- If painful, aspiration needed.

De Quervain's Disease

- **Stenosing tenovaginitis** of the tendon sheath of **abductor pollicis longus** and **extensor pollicis brevis** (at **base of thumb**).
- If the wrist is passively adducted or thumb is ulnar deviated, the patient winces with pain (**Finkelstein's test**).
- Also **wringing of clothes** and **lifting a teapot** cause pain; NSAID's or hydrocortisone injection around tendon.

Dupuytren's Contracture

- Localized **painless, progressive thickening and contraction of palmar fascia**, often bilateral and symmetrical; **nodules in the fascia are the earliest sign**; **ring finger is affected MC**.
- A/w **cirrhosis**, **phenytoin use**, **Peyronie's disease**, **alcoholism**, **AD**.
- **Huesten's table top test**—if patient cannot place his palm flat on a flat surface, surgical referral is wise.
- Surgery is performed when the **MCP joint contracture exceeds 30 degrees** or when the **PIP joint has any degree of contracture** OR if there is **neurovascular damage to the finger**.

Extraplantar manifestations of Dupuytren's contracture

- **Garrod's pads**: Thickening over dorsal aspect of PIPs
- **Peyronie's disease**: Thickened plaques in shaft of tibia
- **Ledderhose's disease**: Thickened plantar fascia, but no contractures

Trigger Finger/Thumb

Constriction of the **fibrous digital sheath** occurs so that free gliding of contained flexor tendon does not occur (**stenosing tenosynovitis** of flexor tendon).

Plantar Fasciitis

It is due to a sharp bony spur at attachment of plantar fascia.

Supraspinatus Tendonitis

Painful arc syndrome affects middle aged and old people, predominantly **males**. Localized tenderness over insertion of supraspinatus tendon.

Achilles Tendonitis

Pain at insertion of Achilles tendon; due to unaccustomed walking or ill-fitting shoes. **MC tendon to rupture**

Frozen Shoulder (Adhesive Capsulitis)

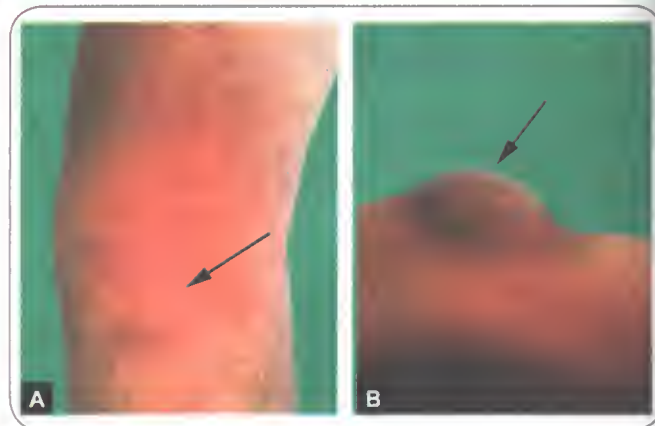
- **Periarthritis shoulder**; stiffness and pain which is worst at **night**; more common in perimenopausal women, **diabetics**.
- Pathognomonic sign: **Loss of external rotation** with the elbow by the side of the trunk.
 - Self-limiting disease lasting for 1–3 years.

COMMON BURSITES

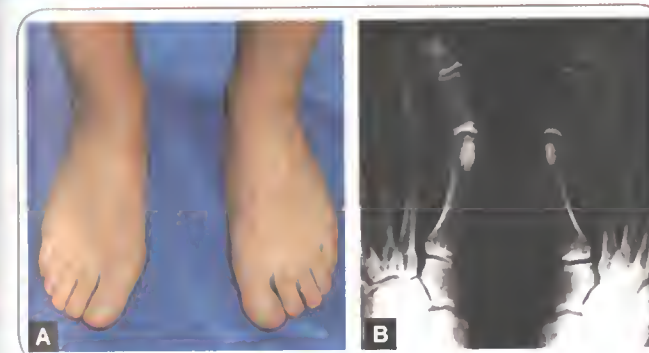
Housemaid's knee	Prepatellar bursitis
Clergyman's knee or Vicar's knee	Infrapatellar bursitis
Weaver's bottom	Ischial bursitis
Tailor's ankle	On lateral malleolus
Bunion (Hallux valgus)	On great Toe
Popliteal cyst	Morrant Baker's cyst

EXTRA EDGE

- **Hallux valgus**: Lateral deviation of great toe (metatarsophalangeal joint of first toe); 'bunionette' involves the 5th metatarsal.



Figs 20.17A and B: A. Prepatellar bursitis (Housemaid's knee); B. Infected infrapatellar bursitis (Clergyman's knee)



Figs 20.18A and B: A. Bilateral hallux valgus deformity; B. Radiographs of hallux valgus deformity

TYPES OF OSTEOCHONDRITIS

Crushing (due to avascular necrosis)	
HiP joint	Perthe's
Metatarsal	Frieberg (Fried Meat)
NavicuLAR	KohLe(A)R
Lunate	Kienbock (Keen lunatic)
Thoracic Spine (presents as adolescent kyphosis)	Scheurmann's (Sure man, nice T Shirt!)
Capitulum	Panner's (PanCap)
Traction epiphysitis (chronic strain injuries)	
Tibial Tuberosity	Osgood-SchlaTter
Calcaneum	Sever (Severely Calculative Calcaneum!)
Lower pole of patelLA	Sinding-Larsen's
Splitting (osteochondritis dissecans)	
Femoral condyles	-
Elbow (capitulum)	-
Ankle (talus)	-

EXTRA EDGE

- MC site of osteochondritis dissecans around the knee is the **lateral part of medial femoral condyle**.

SALTER AND HARRIS CLASSIFICATION

Salter and Harris classification is for epiphyseal (growth plate) injuries.

Type	Injury
I	Separation of epiphysis from metaphysis but without fracture
II	Separation, but with fracture of a small triangular piece of metaphysis (Thurston-Holland sign , shiny corner sign)

Contd...

Contd...

Type	Injury
III	Intraarticular fracture extending from joint surface through growth plate with separation of the portion
IV	Intraarticular fracture, the line going through the plate and through part of the metaphysis
V	Severe end-on crush

EXTRA EDGE

- Salter Harris **type VI injury** = **ablation of perichondrial ring** as in lawn mower blade and degloving injuries. Perichondrial ring is present at the distal end of metaphysis.

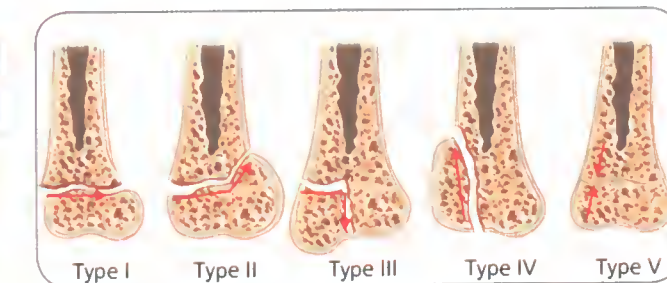


Fig. 20.19: Pictorial representation of the physeal injuries based on Salter and Harris classification



Fig. 20.20: The Salter and Harris type II physeal injury involving the base of the proximal phalanx of the index finger

SHOULDER CONDITIONS

Shoulder Dislocation

MC of shoulder dislocation

- MC joint in human body to **dislocate**
- MC in **Adults**
- MC type is **Anterior (anteroinferior) dislocation**
- MC joint to undergo **recurrent dislocation**

- Fall on outstretched hand with shoulder **abducted, extended** and **externally rotated** is common mechanism of anterior dislocation.
- **Luxatio erecta** is rare type where the head of humerus lies in subglenoid position.
- **Bankart's** lesion (anterior inferior labrum is torn).
- **Hill Sach's** lesion (indented compression fractures at the **posterolateral** part of the humeral head associated with anterior shoulder dislocation).
- Clinically:
 - Patient enters casualty with **shoulder abducted and elbow supported with opposite hand**.
 - **Dugas test**—Inability to touch opposite shoulder.
 - **Hamilton ruler test**—It is possible to place a ruler on the lateral side of the arm touching the acromion and lateral condyle of humerus simultaneously due to flattening of shoulder.
 - **Callway's test**—Increased vertical circumference of axilla compared to normal side.
 - **Positive apprehension test**: With forced abduction and external rotation, patients experiences apprehension (a sense of impending doom).
 - 'Stryker Notch view' is necessary for X-ray.
- Treatment:
 - Reduction of dislocation by
 - **Kocher's maneuver** = **T**Raction, **E**xternal **R**otation, **A**DDuction, **I**nternal **R**otation; ('Treat ERRors with ADDitional Responsibility!').
 - **Hippocrates maneuver** (with foot in axilla);
 - **Stimson's maneuver** (least traumatic method).
- Early complication—Injury to **axillary N** (causing loss of sensation in upper lateral aspect of arm—'regimental badge anesthesia'); late complication—**recurrent dislocation**.
- Anterior dislocation = TUBS = Traumatic, Unilateral, Bankart's, Surgery (**Putti Platt operation, Bankart's operation**).

Atraumatic instability of shoulder (AMBRI)

- **A**traumatic
- **M**ultidirectional
- **B**ilateral shoulder instability
- **R**ehabilitation is the mainstay for treatment
- **I**nferior capsular shift surgery is rarely required

EXTRA EDGE

- **O'Brien test**: Performed to rule out labral cartilage tears that often occur following a shoulder subluxation or dislocation; O'Brien test can also be used to identify Acromioclavicular joint pathol.
- **Habitual dislocation**: Voluntary subluxing the shoulder joint without pain due to joint laxity; they may be doing it as a party trick!

Posterior Shoulder Dislocation

- Posterior shoulder dislocation is a/w **Electric shock or Epilepsy (PEE)**.
- Arm is held in **adduction** and **internal rotation**.
- X-ray features:
 - **Light Bulb sign**: Humerus head fixed in internal rotation (seen in all views—AP; scapular Y and axillary views).
 - 'Trough line sign'; 'rim sign' and 'loss of crescent sign'.



Fig. 20.21: Loss of elliptical overlap as well as 'Empty glenoid sign' suggestive of posterior dislocation of the shoulder. This patient was a known epileptic and sustained this dislocation in an episode of seizure

Rotator Cuff Injury

Rotator cuff tendons

- Supraspinatus
 - Infraspinatus
 - Teres minor
 - Subscapularis
- (**SItS**; small 't' for teres 'minor')

- **Risk factors for rotator cuff tear**: Age > 40 years, Degenerative changes in elderly, Overuse requiring repetitive and excessive over head movements (including swimming, tennis players, etc).
- **Subscapularis tendon** has been called the '**forgotten tendon**' of rotator cuff; **subscapularis tear** is seen by the '**comma sign**' on arthroscopy.
- Pain, **tenderness at deltoid** and over anterior humeral head, difficulty lying on shoulder, ↓ **internal rotation**, crepitation.



Figs. 20.22A to D: (A and B) Extension type of supracondylar fracture; (C and D) Flexion type of supracondylar fracture. Note the site of the fracture and direction of the fracture line. The site of the fracture is just above the condyles. The directions of fracture lines are opposite to each other. In extension type it is obliquely upwards and backwards. In flexion type it is obliquely upwards and forwards

- X-rays changes: ↓ subacromial space, ↓ 6 mm; Anterior spurring of ACM joint; Humeral head degeneration; Sclerotic inferior acromion (**eyebrow sign**); Hooking of acromion.
- 'Single contrast arthrogram' is 'gold standard' in diagnosing rotator cuff tears.

Treatment

- Conservative treatment: Heat massage, NSAIDs, local steroid injection
- If conservative treatment fails for 3 months then **Arthroscopic repair** with **subacromial decompression**.
- For **irreversible tear of rotator cuff**—**Reverse total shoulder arthroplasty** (replacement) is done.

Signs of rotator cuff injury

- **Impingement sign**—Pain and weakness on abduction and internal rotation: **Neer's**; **Hawkin's** and **Jobe's** (empty can) tests.
- **Drop arm test** in which the patient is unable to maintain his or her arm outstretched once it is passively abducted. If the patient is unable to hold the arm up once 90° of abduction is reached, the test is positive.
- **Subscapularis tendon insufficiency**: **Lift-off test** (patient asked to place his hand of the affected arm on his back and unable to lift off the dorsum of the hand from the back); **Napoleon's Belly-press test**; '**Bear hug**' test.

Fracture Shaft of Humerus

- May occur by **direct injury to arm** or **indirect twisting or bending force** as a fall on outstretched hand.

- Can occur in **ALL patterns**—**Transverse, oblique, spiral, comminuted**, etc.
- May be **open** (humerus is surrounded by muscles—incidence of compound fractures is low) or **closed**.
- **Lateral angulation is common** due to abduction of proximal fragment by **deltoid muscle**.
- Presents with pain, deformity, swelling, etc. **Wrist drop** occurs if **radial nerve** is injured; # **Humerus** is **MC cause of wrist drop**.
- Treat with immobilization—**U-slab, hanging cast**, chest arm bandage (in children < 5 years).
- **Union occurs early** due to rich blood supply, some degree of **malunion is undetectable** due to thick muscle cover.

Fracture Surgical Neck of Humerus

- Often in elderly women, minimal symptoms, immobilize with **triangular sling**.
- MC used classification for fracture of **proximal humerus** is the **Neer 4 part** classification.

Fracture Greater Tuberosity of Humerus

- Usually **undisplaced and comminuted**; immobilize with **triangular sling**; **painful arc syndrome** and shoulder stiffness are usual complications.

Fracture clavicle

- Only long bone with **membranous ossification**; only **bone which connects the shoulder girdle to the trunk**.
- MC site of # is at **junction of outer and middle one-third**;
- Results from fall on shoulder or outstretched hand;

Contd.

Contd...

Fracture clavicle

- # unites readily even if widely displaced—**triangular sling** sufficient in most cases;
- **Figure-of-8 bandage** necessary in young adult with displaced #;
- Complications include **injury to subclavian vessels** or brachial plexus, shoulder stiffness.
- Erosion of distal clavicle a/w rheumatoid arthritis and hyperparathyroidism.

Fracture Scapula

Uncommon, **unimportant** since patients recover well without much treatment; mostly undisplaced # since fragments are held in place by surrounding muscles; **triangular sling is sufficient in most cases.**

ELBOW CONDITIONS**'Elbow'****Tennis elbow (Lateral epicondylitis)**

- Inflammation where the **common extensor tendon** arises from lateral epicondyle of humerus.
- **Cozen's test** – Pain at the lateral epicondyle when the patient extends his clenched fist against resistance.
- **Mill's Maneuver** – Pain at the lateral epicondyle when patient's wrist is passively flexed with forearm is pronated. This gives rise to severe pain at attachment of common extensor tendons.

Golfer's elbow

- **Medial** humeral epicondylitis

Student's elbow

- **Olecranon bursitis** (goose egg swelling at the tip of the elbow)

Pulled elbow/Nursemaid's elbow

- **Subluxation of the head of radius** from its encirclement by annular ligament in **young children (< 6 years)**; occurs from sudden pull on upper limb by adult as to prevent from falling or trying to carry with one hand

Little leaguers elbow

- **Avulsion # of medial epicondyle of humerus**

Supracondylar Fracture of Humerus

- Serious **childhood #**, often a/w complications; **extension type MC** than flexion type.

- Presents with **pain, swelling, deformity and inability to move elbow** – **unusual posterior prominence of the point of the elbow (tip of olecranon)** because of **dorsal tilt of distal fragment.**
- **'True' supracondylar fracture** is the **type A.**
- Since **fracture is above the condyles**, the **3 bony points relation is maintained** as in normal elbow.
- Displaced # = immobilization in above elbow plaster slab with elbow in 90 degrees flexion.
- **Displaced # = admit and treat immediately.** Closed reduction under GA and above elbow plaster slab with elbow in hyperflexion. If not possible, open reduction and K-wire fixation (See Fig. 20.19).

Complications of supracondylar #**Immediate**

- **Brachial artery injury:** Due to sharp edge of proximal fragment – may lead to Volkmann's ischemia.
- **MC is anterior interosseous nerve injury;** radial nerve can also be injured—usually **transient.**

Early complications

- **Volkmann's ischemia:** Occlusion of brachial A → Ischemia of forearm muscles → muscles supplied by **anterior interosseous A** are most susceptible (since end artery) → **compartment syndrome.** MC involved muscle is flexor digitorum profundus (**FDP**). Clinically, severe **pain** in forearm, **pain in forearm on passively extending fingers (Stretch test), tenderness on pressing forearm muscles.** Treat by **removing** splints, bandages, encourage patient to move fingers, if no improvement within 1 hour, **fasciotomy** is done.

Late complications

- **Malunion: MC complication** – cubitus **VARus (GUNstock)** deformity occurs – treat with **French osteotomy, 'BeVARE of the GUN!'**
- **Myositis ossificans (heterotopic ossification)** usually **within muscles;** MC follows **trauma;** MC in **children/youth;** MC in **elbow**
- **Volkmann's Ischemic contracture:** As a sequel to Volkmann's ischemia.

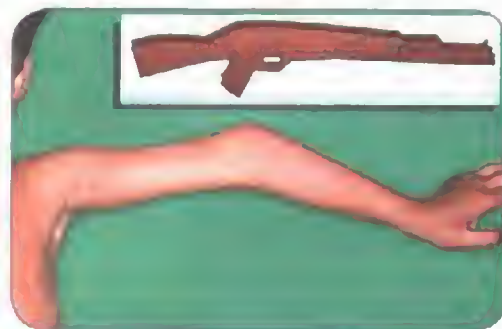


Fig. 20.23: A classical 'Gunstock deformity' of a malunited supracondylar fracture

EXTRA EDGE

- In Volkmann's ischemic contracture **'Stretch pain'** is a sign of impending ischemia **'Paralyzed hand'** is assign of established ischemia **'Volkmann's sign'** flexion of wrist allows passive extension of fingers and dorsiflexion does not.
- Also know, **Compartment syndromes** typically occur in **closed lower limb injuries also;** characterized by severe pain, pain on passive movement of the affected compartment muscles (pain on dorsiflexion of the foot), distal sensory disturbance and, finally, by the absence of pulses distally (a **late sign**).
- Intracompartmental **pressure > 35 mm Hg** is abnormal.

Various Other Upper Limb Fractures and Their Features**# Lateral condyle humerus**

- Common in **children;**
- **Salter and Harris type IV** epiphyseal injury;
- **Accurate operative reduction important** for normal growth of elbow;
- **Cubitus valgus deformity**—diminished growth at lateral side of distal humerus epiphysis results in late ulnar nerve palsy (**tardy ulnar nerve palsy**) because of **friction neuritis** of ulnar N.

Intercondylar # of humerus

- Common in adults due to **fall on point of elbow;** undisplaced # treated by above elbow plaster slab; displaced # by ORIF.

Medial condyle humerus

- More common than # lateral condyle; commonly a/w **posterior dislocation of elbow.**

Dislocation of elbow joint

- **Posterior dislocation MC;** MC is posterolateral a/w # medial epicondyle of humerus; bowstringing of triceps seen; **3-bony points relationship reversed;** a/w **median nerve palsy** and **brachial artery injury.**

Olecranon

- Common in **adults** due to **fall on point of elbow;** treat with **tension band wiring.**

3 Bony Points

- The **3 bony points around the elbow, i.e. the medial epicondyle, the lateral epicondyle and tip of the olecranon** are important landmarks in diagnosis of injuries around the elbow.
- **Normally** in an elbow flexed to 90 degrees, the 3 bony points form a near isosceles triangle, but they lie in a horizontal line in an extended elbow.

- The **base of the triangle** (between the two epicondyles) is the **longest arm.** The side between the medial epicondyle and the olecranon tip is the **shortest.** The **head of the radius,** also considered the **'4th bony point'** can be palpated in a semi-flexed elbow just distal to the lateral epicondyle.

3 bony points maintained in

Supracondylar fracture humerus (since fracture is above the condyles)

3 bony points disrupted in

Intercondylar fracture, medial condyle fracture

3 bony points reversed in

Posterior elbow dislocation

FOREARM AND WRIST CONDITIONS**# Both bones of forearm**

- A/w direct injury to forearm (**lathi blow**)
- Night stick # – # **Ulna** due to direct blow (defensive fracture)
- In children **closed reduction** ↓ GA sufficient
- In adults **ORIF (Open Reduction and Internal Fixation)** is necessary
- Complication include **Volkmann's ischemia** and **cross union** (complete limitation of forearm rotations).

Monteggia # dislocation

- A/w hyperpronation injury
- Fracture of **upper third of ulna** with dislocation of head of radius
- **Hume's #**—High Monteggia # in children
- Very **unstable** injury—Always treated by **OREF** (Open Reduction and External Fixation)
- **Posterior interosseous nerve palsy** is the **MC** nerve injury.

Galeazzi # dislocation

- Fracture of **lower third of radius** with dislocation or subluxation of radioulnar joint;
- **Perfect reduction** essential for complete restoration of all functions—hence called **'fracture of necessity,** i.e. surgery is absolutely necessary!
- Mnemonic: **'MURG'**—**M**onteggia **U**lna, **R**adius **G**aleazzi

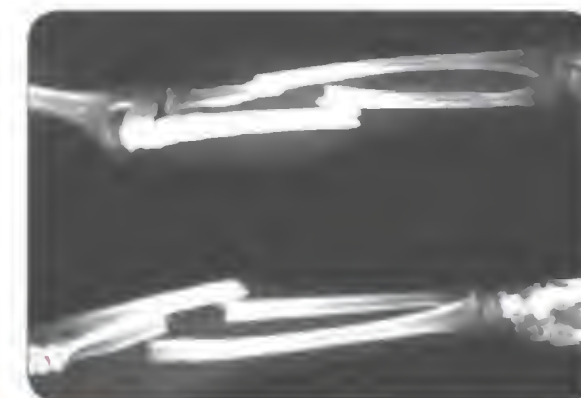


Fig. 20.24: Upper 1/3rd fracture



Fig. 20.25: The maintained relation of superior radioulnar and radiocapitular joints as proven by a line drawn along the long axis of the radius which is continued through the elbow. The relation is lost when there is superior radioulnar joint subluxation or dislocation ('Monteggia fracture')



Fig. 20.26: Galeazzi fractures

Colles' Fracture

- First described by **Sir Abraham Colles** in 1814.
- Fracture of **distal end of radius at the corticocancellous junction** (about 2 cm from the distal articular surface).
- MC fracture in **adults > 40 years**. MC in **women** because of **post-menopausal osteoporosis**.
- Clinically **dinner-fork deformity**, radial styloid process comes to lie at the same level or at higher level than ulnar styloid process.

- **Dorsal tilt** is the most characteristic displacement others are lateral tilt, impaction and supination.
- Treat with **closed reduction and immobilization** in plaster cast for **6 weeks**.
- **Finger stiffness** is the **commonest complication**.
- Colle's # is MC cause of **Sudeck's dystrophy** in upper limb
- Non-operative treatment: **Below elbow cast** in **5 deg flexion** and **5 deg ulnar deviation**; immobilize for 4-6 weeks.
- Operative treatment: K-wire fixation under C arm image intensifier control.

Scaphoid Fracture

- MC in **young adults**; # occurs through **waist of scaphoid**; pain and swelling over radial aspect of hand after fall on outstretched hand.
- **Clinically: Tenderness in scaphoid fossa (anatomical snuff box)**—between tendon of **extensor pollicis longus and brevis**; Tenderness over scaphoid tubercle (Freeland test); Scaphoid compression test (Chen test) may be seen.
- If # strongly suspected and not visible on initial X-ray, it should be **repeated after 2 weeks**.
- Treat with closed reduction and immobilization in **scaphoid cast** for 3-4 months (**glass holding position**). **Avascular necrosis** (of proximal fragment) may occur.

EXTRA EDGE

- **Preiser's disease** = Idiopathic avascular necrosis of scaphoid; Scaphoid = 'boat shaped'



Fig. 20.27: Radiographs of scaphoid fracture showing nature of fracture lines. Horizontal oblique and transverse fractures are considered as stable fractures when undisplaced. Whereas vertical fractures whether displaced or undisplaced are unstable

HAND CONDITIONS

Hand Deformities

- **Accaucher's hand** (obstetrical hand): Tetany or muscular dystrophy
- **Club hand**: Talipomanus
- **Crab hand**: Erysipeloid
- **Frag hand**: Mid palmar space infection
- **Ghaul hand**: Tertiary yaws
- **Griffin claw hand**: Ulnar nerve palsy
- **Marinescu's succulent hand**: Syringomyelia
- **Spade hand**: Acromegaly or myxedema
- **Trident hand**: Achondroplasia
- **Starfish hand**: Achondroplasia
- **Catcher's Mitt hand**: Reflex sympathetic dystrophy syndrome



Fig. 20.28: Clinical features of an achondroplastic dwarf. Note the 'Starfish hand' on one side (Right hand) and 'trident hand' on the other side (Left hand). Also note the presence of a single transverse crease in the palm

Felon

- Infection of the **volar distal fat pad (terminal pulp space)** of the finger usually after **splinter/needle prick injury**; MC involved is **thumb > index** finger.
- MC caused by **Staphylococcus**.
- Local pain and lymphangitis are present, osteitis may occur.
- Treat by incision and drainage; **longitudinally oriented incision** is given to **divide fibrous septa**.
- MC complication is **osteomyelitis**.

Paronychia

- Painful infection of **nail bed**;
- MC due to **Staphylococcus aureus**;
- If suppuration occurs, treat by **incision and drainage** and **antibiotics**.

Tenosynovitis

- Infection within the **flexor tendon sheath** may be the result of spread of adjacent pulp infections or puncture wounds in the flexor creases.
- MC organism is **Staphylococcus aureus**.

Kanavel's Four Cardinal Signs

Tenderness over the involved sheath, rigid positioning of the **finger in flexion** (most important), **pain on attempts to hyperextend** the fingers and **swelling** of the involved part are used for diagnosing **infectious tenosynovitis**.

Bunnell's 'No Man's Land'

A fanciful term for the fibrous sheath of the flexor tendons of the hand, specifically in the zone **from the distal palmar crease to the proximal interphalangeal joint** – corresponds to **zone II of hand**.

Parona's Space

A space **between the pronator quadratus deep and the overlying flexor tendons of the forearm** that is continuous through the carpal tunnel with the medial central palmar space.

HIP CONDITIONS

Pelvic Fractures

- Occurs in **vehicular injuries**, usually with other multiple #s.
- **Marvin Tile's classification** into type A (isolated #) and types B and C (pelvic ring #).
- **Ischiopubic rami # is commonest** of the isolated #s.
- Clinically, often NO obvious deformity, **pelvic compression test** is useful screening test to detect pelvic #.
- Treatment consists of **first correction of hypovolemic shock** (iliac wings are very vascular).
- For injury with **minimal displacement**, **absolute bed rest** for 3-4 weeks.
- For injury with displacement > 2.5 cm, **closed reduction necessary** and maintained in position by **Hammock sling/external fixator, plaster spica**. Injury with vertical displacement most difficult to treat.
- **Complications**:
 - **Rupture of urethra** (**membranous MC**, with **blood per urethra, perianal hematoma and distended bladder**);

- **Rupture of bladder** (usually *extraperitoneal* and urine extravasates into perivesical space).

Fracture Neck of Femur (Intracapsular, Unsolved #)

- MC mechanism in elderly is due to *fall*.
- In young, significant *high force trauma* is required.

Garden classification (according to degree of displacement)

- Non-displaced
 - Grade I is an incomplete or valgus impacted fracture.
 - Grade II is a complete fracture without bone displacement.
- Displaced
 - Grade III is a complete fracture with partial displacement of the fracture fragments.
 - Grade IV is a complete fracture with total displacement of the fracture fragments.

- **Classification according to level of the fracture line in the neck** as follows: *Subcapital; Transcervical; Basal*.
- *Subcapital fractures* are classified along below two continuums.

Pauwels classification	Linton classification
Type I has an obliquity ranging from 0 to 30 degrees	Stage I: Incomplete fracture
Type II has an obliquity ranging from 30 to 50 degrees	Stage II: Complete but undisplaced fracture
Type III has an obliquity of 70 or more degrees	Stage III: Complete, partially displaced fracture
	Stage IV: Displaced and totally free fracture

- In *children*, proximal femoral fractures are classified as per *Delbert's classification*—*transcervical #* is MC.

EXTRA EDGE

- *Evans and Boyd and Griffin classification* are used for intertrochanteric fracture.

Clinical Features

- *Elderly person (osteoporotic females) with a h/o trivial fall (slip in bathroom) and inability to walk*.
- Injured leg lies in a position of *external rotation* and there is *shortening of the leg*.
- *Tenderness over the anterior and lateral aspects* of the hip joint.
- The *greater trochanter is elevated* on the injured side.
- *Pain in groin* (in femoral triangle area).
- *All movements are extremely painful* except in the rare case of an impacted type of fracture.

Treatment

- *Surgery within 24 hours is the treatment of choice*.
- In patients < 60 years = *Open reduction and internal fixation* under radiological control using *multiple cancellous screws (MC method) or dynamic hip screw*.
- In patients > 60 years = *hemiarthroplasty* (removing the head of the femur and replacing it by metal prosthesis like *Austin Moore's prosthesis*). This enables the patient to be ambulant and start early weight bearing.
- In patients > 60 years with *preexisting hip arthritis* = *total hip replacement*.
- After surgery—early ambulation to *prevent DVT and decubitus ulcers*.
- The *Austin Moore's prosthesis* was designed for use *without bone cement*; using a fenestrated stem to allow 'selflocking' of the prosthesis in the proximal femur.
- *Occult fracture neck of femur* is diagnosed by *MRI*.



Fig. 20.29: Bilateral hemiarthroplasty using Austin Moore's prosthesis done for a case of bilateral fracture neck femur. First time patient sustained the fracture in the right hip and an year later in the left hip



Figs 20.30A and B: A. Dynamic hip screw and barrel plate. B. Jewett nail



Figs 20.31A and B: A. An Austin Moore's prosthesis; B. A Thompson's prosthesis. These are commonly used in fracture neck of femur for replacement hemiarthroplasty. Note the fenestrations in the stem of Austin Moore's prosthesis for the ingrowth of bone and initiation of a self-locking process. This is used when *calcar femorale* is sufficient. When *calcar femorale* is deficient, Thompson's prosthesis with bone cement is used

Differences between Fracture Neck of Femur and Intertrochanteric Fracture

	Fracture neck of femur	Intertrochanteric fracture
Age	> 50 years	> 60 years
Sex affected	F > M	M > F
Injury	Severe	Moderate
Ability to walk	May walk in impacted fracture	Not possible
Pain	Mild	Severe
Swelling	Nil	Severe
Ecchymoses	Nil	Present
Tenderness	In <i>Scorpio's</i> triangle	On greater trochanter
External rotation	< 45 degree	> 45 degree
Shortening	Less than 1–2 cm	> 2 cm
Treatment	Internal fixation always	Can be managed by traction; BUT NOW open reduction with internal fixation is the Rx of choice.
Complication	Nonunion	Malunion

Causes of Non-union of # Neck of Femur

- Avascularity of head of femur
- Continuous synovial bathing (inhibitory effect of synovial fluid)
- Lack of *cambium layer* in the periosteum of the neck (this is the layer that normally produces callus)
- Inadequate immobilization, inaccurate reduction, poor internal fixation.

Hip dislocation

- *Posterior Hip* dislocation MC; occurs with *dashboard injury* in cars.
- Deformity is *Flexion, Adduction, Internal Rotation (FADIR)* with shortening of the leg.
- On X-ray *Shenton's line* is broken.
- *Stimson's maneuver* is the least traumatic method for reducing *posterior dislocation of hip*.
- *Allis and Reverse Bigelow's* method: Used for reduction of *anterior dislocation of hip*.

Also know

- *Anterior dislocation*: Limb shortening is a/w flexion/abduction/external rotation deformity (FABER).
- *Central dislocation*: Limb shortening and abducted and internally/externally rotated.

Shaft of Femur

- Aka diaphyseal fracture of femur.
- A/w *major trauma/RTAs*.
- May be a/w pelvic fractures; in *children* minimal displacement BUT in adults there is marked displacement.
- *Blood loss* upto 1.5 l. can occur and may cause *hypovolemic shock*.
- Types: Transverse, spiral, oblique, segmental and comminuted.
- Clinically: Thigh swelling, pain, abnormal mobility.
- Immediate Rx: Immobilization and IV fluids.
- Definitive treatment: Closed or open reduction with *internal fixation (locked IM nailing)*. Good apposition of fragments with > 75% contact is essential for union.
- In children < 2 years *Gallow's traction* may be used.
- Complications:
 - Hypovolemic shock due to hemorrhage
 - *Fat embolism*
 - Injury to *femoral artery and sciatic nerve*.

Winquist and Hansen Classification of # Shaft of Femur

- Type 0** No comminution
- Type 1** Minimal comminution
- Type 2** > 50% cortical contact between the two fragments exists
- Type 3** < 50% cortical contact between the two fragments exists
- Type 4** Segmental fracture with no contact between proximal and distal fragment

EXTRA EDGE

- Another Classification for *diaphyseal fracture femur*: Muller AO classification.



Figs. 20.32A and B: A badly comminuted fracture of the shaft of the femur. It is not possible to achieve good apposition of fractured fragments by closed methods, after open reduction and internal fixation by interlocking nailing

Surgical Approaches to the Hip

1. Anterior (Smith-Peterson) approach

- Advantage: *Gluteus maximus and medius remains intact*; less damage to the posterior capsule; Commonly used to access the hip in cases of suspected *septic arthritis*.
- Disadvantage: Not ideal for major reconstructive surgery in adults; Possible *injury to the lateral femoral cutaneous nerve*, which can cause lateral thigh numbness.

2. Anterolateral (Watson James) approach

- Advantage: *Gluteus maximus and medius remains intact*; less damage to the posterior capsule.
- Disadvantage: Potential damage to the anterior fibers of *gluteus medius* while exposing the femoral neck.

3. Direct lateral (Hardinge) approach

- Advantage: Posterior capsule and muscles are not cut (*lower dislocation rate*).
- Disadvantage: Repaired *abductor muscles* must be protected after the surgery by limiting the patient's weight bearing status.

4. Posterior (southern, Kocher-Langenbeck) approach

- Advantage: *Abductor muscles NOT injured* and *excellent exposure* of proximal femur and acetabulum.
- *MC approach* for a total hip replacement today.
- Disadvantage: Posterior capsule and muscles are cut during the approach.

More One Liners

- Hip dislocation if delayed >12 hours increases risk of avascular necrosis 3 fold.
- # that enters the greater sciatic notch can lacerate the *Superior gluteal artery*.
- Metaphysis is *intraarticular* in hip, shoulder.
- Lateral side of the medial femoral condyle is the MC site of osteochondritis dissecans.
- *Nelaton's line* – A line drawn from the most prominent part of the ischial tuberosity to the tip of the anterior superior iliac spine.
- *Schoemaker's line* – Line from the tip of the greater trochanter to the anterior superior iliac spine. If prolonged anteriorly will reach the umbilicus of the patient.
- *Bryant's triangle*: A triangle formed by the anterior superior iliac spine (ASIS), the greater trochanter and a line drawn vertically downwards from the ASIS.
- *Ludloff sign*: Inability to flex the stretched leg when the patient is seated. Seen in avulsion fracture of the lesser trochanter.
- Internal rotation is often the first movement to be restricted by hip disease.

KNEE CONDITIONS

Anterior cruciate ligament tear (ACL)

- *MC injured ligament* of knee; ACL connects the *posterior aspect of the lateral femoral condyle* to the *anterior aspect of the tibia*.
- ACL has two parts: *Anteromedial bundle* tightens in *flexion* while *posterolateral bundle* tightens in *extension*.
- Its main function is to *control anterior translation of the tibia on the femur* – *Lachman test* and/or *anterior drawer test* finds pathologic anterior tibial translation.

Contd.

Contd.

Anterior cruciate ligament tear (ACL)

- It also provides *rotational stability of the tibia on the femur* – '*Pivot shift*' test is used to *determine the amount of rotational laxity* of the knee.
- ACL injury commonly results from *valgus blow to the knee* (from *lateral side*) or *sudden deceleration* (fracture passing through *intercondylar eminence* can injure the ACL).
- Presents with a '*popping sound*' in the knee; patient may complain of *knee instability* or '*giving way*'.
- *MRI* is best method; Plain X-ray – *Segond fracture* is an *avulsion # of the knee* which involves the *lateral aspect of the tibial plateau*, and is *MC a/w ACL tear*; '*lateral capsular sign*' on AP view of knee.
- Conservative treatment or arthroscopic repair.

Posterior cruciate ligament tear (PCL)

- *Strongest ligament* of knee; main function of the PCL is to prevent posterior translation of the tibia on the femur.
- PCL injury indicates *significant trauma* and commonly a/w ACL, MCL and posterolateral corner injuries; 1/3 cases have *neurovascular injuries*.
- Lear seen during *falls on flexed knee* and during *dashboard injuries* in motor vehicle accidents.
- *Sag sign*: *posterior drawer test* and positive quadriceps active test help in diagnosis; patients have *difficulty in walking*.
- Imaging – *MRI* is best; X-rays nonspecific; '*magic angle artefact*' may be seen in *MRI*.
- Conservative treatment or arthroscopic repair
- Combination PCL (posterior cruciate ligaments) and *Posterolateral corner (PLC) injuries* are best determined by the *tibial external rotation (Dial)* test with the knee in both 30 and 90 degrees of flexion.

Collateral Ligament Tear

- *Medial collateral ligament injury* is seen after *direct lateral blow to the knee*; commonly a/w ACL injuries.
- *Valgus stress test* for *medial collateral ligament*
- *Varus stress test* and *Cabot's stress* maneuver used for *lateral collateral ligament*.
- Conservative treatment with *Hinge brace*.

Meniscus tear

- *Menisci* are *shock absorbers* of the knee.
- *Acute trauma* or more commonly due to *degeneration* seen with ageing.
- *Medial meniscus* is *larger* in diameter; has a *narrow body* and is *less mobile*.
- *Lateral meniscus* is *smaller* in diameter, has a *wider body* and is *more mobile*.
- *Medial menisci* injured 3 times *MC*. M > F
- *Joint line pain* and *pain with deep squatting*
- *Twisting of the knee* when the knee is bent (flexed) leads to meniscal injury; patient may experience a clicking sensation while walking. A sensation of the knee giving way or even a '*locked*' knee.

Diagnosis

- Meniscal palpation tests: *McMurray test* – patient supine with hips flexed 90° and knee fully flexed, maneuver foot into abduction-adduction and external-internal rotation while palpating joint line for a click; also *modified McMurray test*; *Bragard's test*; *Steinman's second test*; *figure of 4 meniscus stress maneuver*.
- Meniscal rotation tests: *Apley's grinding test*; *Thessaly test*; *Bahler's test*; *Squat test*; *Duck walking test*; *Merke's test*; *Helfet test*; *Peyr's test*; *Steinman's first test*.
- *MRI* is best diagnostic test: *Bright meniscus on T2* means a *torn meniscus*.
- Treat with arthroscopic repair.

EXTRA EDGE

For explanation of all above meniscal tests – go to this link: <http://www.biomedcentral.com/1758-2555/3/25>.

Fracture Patella

- May results from *direct force* (*comminuted or stellate #*) and from *indirect force* (2 part #).
- Pain, swelling and *crepitus* over knee, extensor lag (*unable to lift leg with knee in full extension*).
- X-ray '*skyline view*' may be required in undisplaced #;
- Treat with *tension band wiring* (like # *olecranon*).

O'Donoghue's Unhappy Triad Knee

- *Medial Meniscal* tear
- *Anterior Cruciate ligament* (ACL) tear

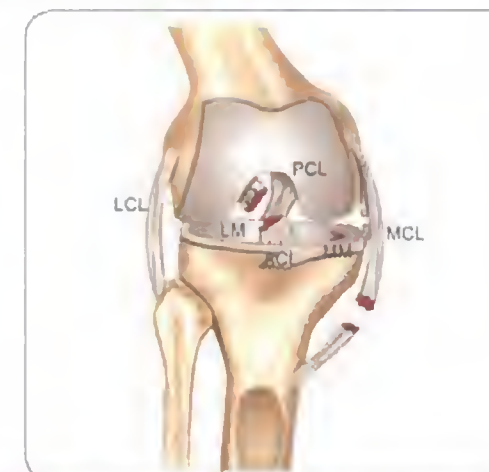


Fig. 20.33: 'Terrible/unhappy triad' of O'Donoghue. In this medial collateral ligament, anterior cruciate ligament and medial meniscus are damaged. Medial collateral ligament—MCL; Lateral collateral ligament—LCL; Anterior cruciate ligament—ACL; Posterior cruciate ligament—PCL; Medial meniscus—MM; Lateral meniscus—LM

- Medial Collateral ligament (MCL) tear/strain
'My Mental Aunty Cut My Cake!'

Blount's Disease

- **Tibia vara;**
- MC in West Indies;
- Growth of the **medial half of the proximal tibial epiphysis** is retarded;
- **Siffert-Katz sign**—Knee is stable in full extension but the medial femoral condyle may sublux posteromedially (into the depressed media; tibial plateau) at 10–20 degrees in flexion.

More One Liners

- **Snow storm knee** - **synovial chondromatosis**
- In **knee dislocation**—Popliteal artery, vein and peroneal nerve injury can occur.
- **Runner's knee:** Pain of **patellofemoral joint**.
- **Tension band wiring** is used in treatment of fractures of **patella and olecranon**.
- Two **radiological indices** used to determine position of **patella** are: **Insall Salvati Index** and **Blackburne-Peel Index**.
- **Bulge sign** can be used to detect < 30 mL effusions in the knee joint.
- In '**bounce home**' test of knee joint end feel may be described as 'bony', 'springy' or 'firm'.
- Proximal or **high tibial osteotomy** is contraindicated if more than 20 degrees of correction is needed.

LEG AND ANKLE CONDITIONS

Shaft of tibia and fibula

- May result from **direct force** (road accidents) or indirect injury (**torsional force**);
- **Pemister grafting** (a type of bone grafting performed without disturbing the sound fibrous union at # site).
- Complications include **delayed and non-union** due to precarious blood supply of distal third of tibia, **extensive skin loss**.
- Varus or valgus **angulation of 5 degrees** on AP view is acceptable after reduction of tibial shaft fracture.

Ligaments of ankle

- **Medial collateral ligament (deltoid ligament):** Superficial (tibio calcaneal) and deep (tibiotalar) part.
- **Lateral collateral ligament:** Weak ligament and often injured. Has 3 parts – **anterior talofibular (MC cause of sprained ankle - usually due to forced inversion with plantar flexion)**, calcaneofibular and posterior talofibular.

Calcaneum

- Also known as '**Don Juan fracture**' or '**Lover's fracture**'
- Due to fall from a height **onto the heels** (e.g. thief jumping from first floor of a house).
- Ankle movements are normal but **unable to bear weight on the heel**.
- **Lateral X-ray of heel** reveals #.
- **Bohler's angle** decreased and '**crucial angle of Glissano**' increased.

Talus

- **Talus** is the only bone of the foot **without any muscular attachment**.
- Talus is Aka 'astragalus'.
- The **Hawkins sign** is a subchondral radiolucent band in the talar dome that is indicative of viability at 6 to 8 weeks after a talus fracture; it is a **good indicator of talus vascularity** following fracture.

More High Yield Points

- **Ankle sprains** are the **MC sports injuries** seen in outpatient clinics.
- The MC mechanism of injury is an inversion and plantarflexion sprain, which injures the **anterior talofibular ligament**.
- **Special stress tests for the ankle** include the **anterior drawer test** and **subtalar tilt test**.
- **Oblique ankle X-ray view** is **mortise view**.
- **Ottawa Ankle Rules** are clinical prediction rules to guide the **need for radiographs**.
- Immediate treatment of an ankle sprain follows the **MICE: Modified activities, Ice, Compression, and Elevation**.
- **Lauge Hansen** classification is for ankle injuries.
- **Calcaneum** is the **MC fractured tarsal bone**.
- Commonest indication for **ankle arthrodesis** is **post-traumatic arthritis**.

SPINAL CONDITIONS

Prolapsed Intervertebral Disc

- Pathology consists of three stages:
 - Nucleus (pulposus) **degeneration**
 - Nucleus **displacement** (protrusion, extrusion and finally sequestration)
 - Stage of **fibrosis**.
- The site of exit of the nucleus is usually **posterolateral**.
- **MC site** of disc prolapse in lumbar spine is between **L4-L5** and in cervical spine between **C5-C6**.

- MC symptom is **low back pain** with/without pain radiating down the back of the leg (sciatica).
- A **positive straight leg rising test (SLRT)** at 40 degrees or less suggests nerve root compression. More important is a **positive contralateral SLRT**.
- **Lasague test** is positive.
- **Nerve root** affections are as shown in following table.
- **MRI** is the inv of choice.
- **Schmorls' node** - is a radiological manifestation of an extrusion of nucleus pulposus into the body of a vertebra.
- **Myelography** not routinely done; can show the **root cut off sign**.
- Main treatment is conservative by rest and analgesics.
- Indications for surgery are: (1) Cauda equina syndrome (2) Severe sciatic tilt.
- Procedures for removal of intervertebral disc: **Fenestration**; **laminotomy**, **laminectomy** and **hemilaminectomy**.
- **Chemonucleolysis:** Enzyme chemopapain injected into disc to dissolve it under X-ray guidance.
- **Percutaneous discectomy** - Disc is removed using an endoscope.
- The **H-reflex** on stimulation of the tibial nerve in the popliteal fossa is routinely used in the diagnosis of **first sacral (S1) nerve-root radiculopathy**.

Nerve root affected	Motor weakness	Sensory Loss
S1	Weakness of plantar flexors of foot	Over lateral side of the foot
L5	weakness of EHL + dorsiflexors of the foot	Over dorsum of the foot and lateral side of the leg
L4	Weakness of extensors of the knee	Over great toe and medial side of the leg



Fig. 20.34: 'Straight leg raising test' being performed. In this it is negative and the leg can be raised up to 80°

Three-Column Concept of Spine

- **Francis Denis', three-column concept** divides a spinal segment into three parts:
 - **Anterior** column comprises the anterior longitudinal ligament and the anterior half of the vertebral body.
 - **Middle** column comprises the posterior half of the vertebral body and the posterior longitudinal ligament.
 - **Posterior** column comprises the pedicles, the facet joints and the supraspinous ligaments.
- Generally, if **two or more** of these columns are damaged, then the spine is unstable. If only one column is disrupted, the spine is stable.

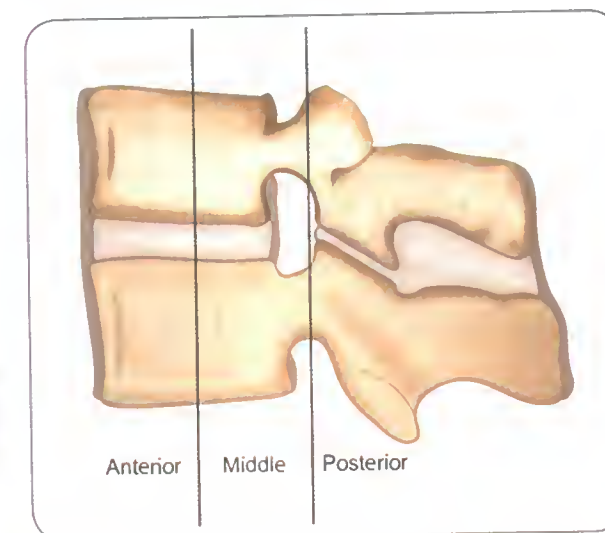
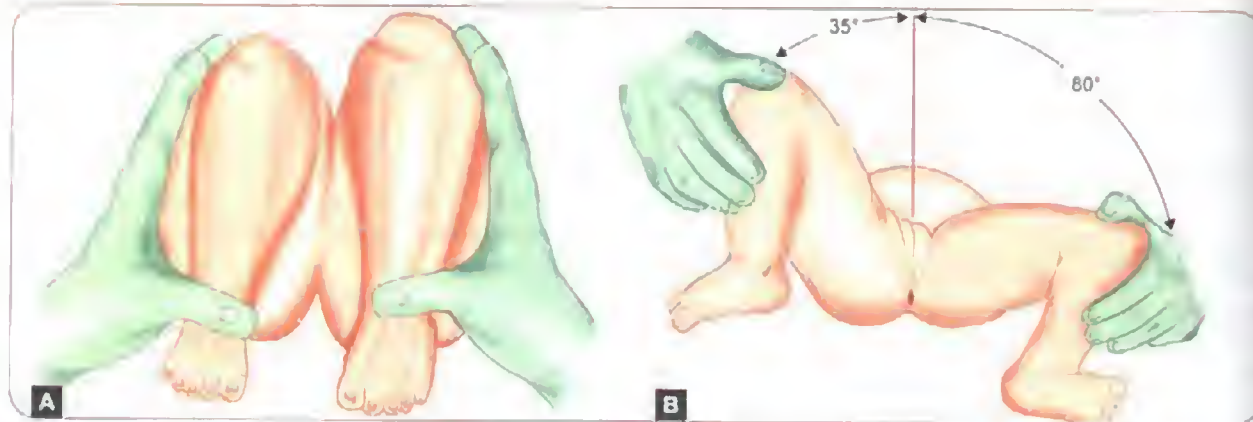


Fig. 20.35: Denis' three-column concept

Spinal Trauma

- In developing countries **fall from a height** is **MC mechanism** of spinal injury in developed countries it is RTA.
- Types of spinal injury are:
 - **Flexion type (MC);** a/w compression #; stable
 - **Flexion-rotation injury (worst type** since a/w high incidence of neurological damage)
 - **Vertical compression injury;** a/w **burst #**
 - **Extension injury (MC in cervical spine);** a/w avulsion # of anterior lip of vertebra
 - **Flexion distraction injury** (due to seat belts); **Chance #** - horizontal # through vertebra (body, pedicles, laminae) due to sudden deceleration with lap-only seatbelt; usually L1 or L2
 - Direct injury and muscle contraction injury (rare).



Figs 20.36A and B: A. Asymmetry in the level of the knees which is known as Allis, Perkins or Galeazzi sign. On the involved side in unilateral DDH, the knee will be at a lower level; B. Limitation of abduction of the involved tight hip

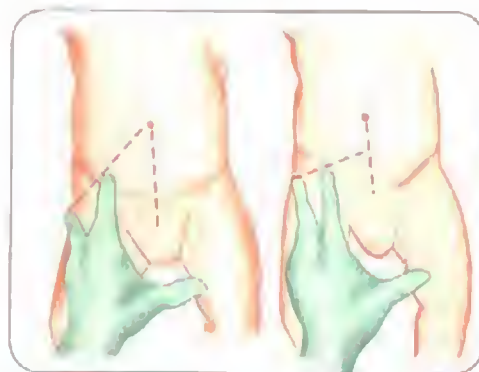
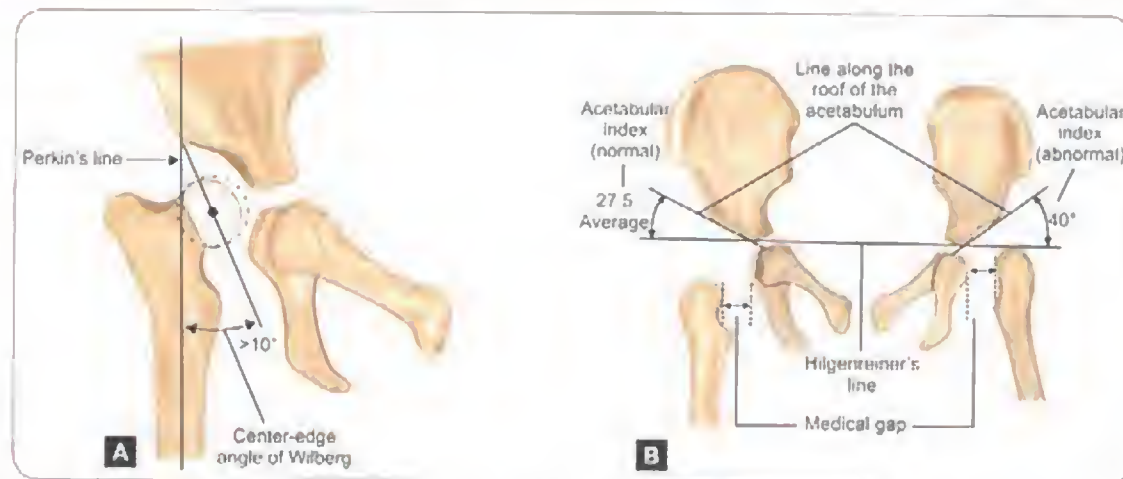


Fig. 20.37: Klisic test. Note the imaginary line cutting through the umbilicus in a normal hip and cutting midway between the umbilicus and the pubis in a DDH



Figs 20.38A and B: A. Center-edge angle of Wilberg: It is an angle formed between the Perkin's line and the line drawn from the lateral iliac crest of the acetabulum passing through the center of the femoral head. In older children (10–13 years) the angle should always be more than 10°; B. Acetabular Index: This is an angle formed between a line drawn along the margin of the roof of the acetabulum and Hilgenreiner's line. Average angle in newborn is about 27.5°. It decreases with age. Medial gap: This is the distance between the inner margin of the tear drop and the inner margin of the neck of the femur. The gap increases in dislocation. Always compared with the opposite hip. Not useful in bilateral cases

- **MRI** is the inv of choice.
- In **acute spinal cord injury**, IV **methylprednisolone** bolus **30 mg/kg over 15 minutes** if administered **within eight hours** of injury followed by maintenance dose infusion of 5.4 mg/kg per hour infused for 23 hours has been shown to improve neurologic outcome up to one year post injury.
- Skull traction with **crutchfield tongs** may be applied.

SCIWORA

- **SCIWORA** = Spinal Cord Injury Without Radiographic Abnormality; i.e. plain X-ray and CT scan are normal BUT **MRI does show** abnormalities.
- Initially described by **Pang**.
- MC seen in **children**; MC seen in **cervical spine**.

Flags in Back Pain

Red Flag	Indicate potential serious pathology
Yellow Flag	Risk factors for chronicity, the psychosocial barriers to recovery
Orange Flag	Psychiatric Issues in patients with back pain
Blue Flag	Occupational issues
Black Flag	Organizational barriers to recovery

More One Liners

- **Dislocation without fracture** can be seen in **cervical spine**.
- **Spurling test**: Involves asking the patient to rotate and extend the neck to one side. The clinician can apply a gentle axial load to the neck. Reproduction of the **cervical radiculopathy** symptoms is a positive sign of nerve root compression.
- **Percutaneous vertebroplasty** was developed in order to increase mobility, stabilize the spine and decrease the pain due to vertebral compression fractures caused by **metastases, hemangiomas and osteoporosis**. Here polymethylmethacrylate (PMMA) is injected into the fractured (compressed) vertebral body.
- **Balloon kyphoplasty**: A small balloon is inflated in the compressed vertebral body to restore its height and alignment.
- Both above procedures are absolutely contraindicated in infection, untreated coagulopathy and healed osteoporotic fractures.
- Erosion of the pedicles (the '**winking owl**' sign) is the earliest radiologic finding of **vertebral tumor**.
- **Earliest reflex** to reappear after **spinal shock** is **hubbocavernosus reflex**.
- There are **31 pairs of spinal nerves** in the body.
- **Atlantoaxial instability** is common in **Down's**.
- Structural scoliosis can be differentiated from postural/scoliosis by **Adam's test**.

CONGENITAL DISORDERS

Congenital Dislocation of Hip

- Aka **developmental dysplasia of the hip**.
- **M:F = 1:6**; **left hip** MC affected; B/L in 1/3; not common in Africans/Asians.
- **Predisposing factors**: **Breech** delivery (Frank breech with hip and knee extended), **hereditary predisposition**, **maternal hormone induced joint laxity**, **arthrogryposis** and **spina bifida**.
- Screening tests in the neonatal period are hip is always **dislocatable** and **reducible** by **Ortolani's** and **Barlow's test** (both are positive).
- In the older child, signs may be:
 - **Delay in walking**;
 - Abnormal **waddling gait** (affected leg is shorter);
 - **Asymmetrical thigh and gluteal folds**;
 - **Higher buttock** on affected side;
 - **Galeazzi's sign** (lowering of the knee on the affected side in a child lying supine with hip flexed to 70 degrees and knees flexed - aka **Allis** or **Perkins sign**)
 - **Limitation of abduction** of hip (early sign); **Telescopy** is positive.
 - **Vascular sign of Narath** - Normally the femoral is palpated against the head of the femur, but in CDH the head of femur is dislocated and there is great difficulty in palpating the artery.
 - **Klisic test**: With the child supine, the index finger is kept over the ASIS and the middle finger over the greater trochanter and an imaginary line is drawn between the two; this line when extended upward cuts through the umbilicus in a normal hip BUT in CDH this line cuts midway between the umbilicus and pubis (Figure 20.37).
- After child starts walking signs may be:
 - **Limb shortening** is pronounced in U/L cases
 - **Trendelenburg gait** in U/L cases and **waddling gait** in B/L cases
 - **Exaggerated lumbar lordosis** sec to flexion contracture at the hip.
- Treatment:
 - **Before 6 months**: Closed reduction; Pavlik harness, Cralg splint or von Rosen splint are used in 1-6 month age group.
 - **Older child > 6 months**: Open reduction
 - **Acetabular reconstruction procedures** include: **Salter's** osteotomy; **Pemberton's** osteotomy, **shelf procedure** and **Chiari's pelvic** displacement osteotomy.

Radiology of CDH

- ▶ In **neonates**, **ultrasound** is the investigation of choice. Useful **only upto 6 months** of age.
- ▶ Plain X-ray: useful **only after 3 months** of age.
- ▶ **Von Rosen view** (hips fully abducted and externally rotated).
- ▶ **Putti's triad**: Absent/small proximal femoral capital epiphysis; lateral displacement of femur and shallow acetabulum with increased inclination of acetabular roof (> 30 degrees).
- ▶ **Shenton's line** extends from the upper curved border of the obturator foramen to the lower border of the neck of femur. In CDH, there is a **break** in this line.
- ▶ **Perkin's line**: A vertical line is drawn from the outer edge of the acetabulum on both sides.
- ▶ **Hilgenreiner's line**: A horizontal line is drawn through the triradiate cartilage.
- ▶ The upper femoral epiphysis normally lies medial to the vertical (Perkin's) line and below the horizontal (Hilgenreiner's) line - i.e. in the **lower inner quadrant**. But in CDH, the epiphysis will lie on the outer aspect of the vertical line and above the horizontal line (i.e. upper outer quadrant).

Congenital Talipes Equinovarus (CTEV)

- **Idiopathic clubfoot**: May be due to raised intrauterine pressure forcing the foot against the wall of the uterus in the position of deformity (mechanical theory); ischemia of calf muscles due to unknown cause (ischemic theory); or due to genetic cause (genetic theory).
- **Primary (Congenital clubfoot)**: Cases where clubfoot may be present since birth include:
 - ▶ Idiopathic (most common type)
 - ▶ Neurogenic—Spina bifida
 - ▶ Dysplastic—Arthrogryposis multiplex congenita (AMC).
- **Secondary (Acquired clubfoot)**: In some diseases a muscle imbalance may result, causing contracture of the posteromedial foot structures leading to a secondary CTEV anytime during life.
 - ▶ Paralytic (Poliomyelitis)
 - ▶ Post-traumatic—contracted scar on posteromedial aspect
 - ▶ Postinfective
 - ▶ Spastic (Cerebral palsy).
- Clinical features of a classic case are:
 - ▶ **Bilateral** foot deformity in 60% of cases
 - ▶ Size of the foot is smaller in unilateral cases, **Heel is small** in size
 - ▶ The foot is in **equinus**, **varus** and **adduction**
 - ▶ **Deep skin creases** on the back of the heel and medial side of sole

- ▶ Bony prominences felt on the lateral side of the foot the head of the talus and lateral malleolus
- ▶ The outer side of the foot is gently convex; there are dimples on the outer aspect of the ankle
- ▶ Dorsum of foot **cannot** touch the shin (anterior tibial surface).
- X-ray:
 - ▶ **Talocalcaneal parallelism** is the radiographic feature of clubfoot.
 - ▶ The **talocalcaneal angle (Kite's angle)** in both AP and lateral views in a normal foot is more than 15 degrees, but in CTEV these are reduced.

Order of correction of deformity in CTEV (ADVERB)

- ▶ **AD** – Forefoot **AD**duction is corrected first
- ▶ **V** – Correction of heel **V**arus next
- ▶ **E** – Lastly correction of hindfoot **E**quinus (**most resistant** to passive correction and the **earliest** to recur)
- ▶ **RB** – If this order is not followed, **R**ocker **B**ottom foot results.

- **Ponseti method of manipulation and casts** to correct CTEV in newborn (NO surgery) is **now used first**. Manipulation is done in the following order to correct the deformity - 1st Cavus, 2nd Adductus, 3rd Varus and lastly Equinus ('CAVE').
- **Manipulation by mother** should begin soon after birth.
- Surgery is indicated for **unresponsive, rigid, recurrent** CTEV - done upto 4 years of age.
- **PMSTR** = PosteroMedial Soft Tissue Release; structures preserved in PMSTR are - **deep deltoid** ligament; **interosseous** ligament; **medial neurovascular bundle**; **dorsal structures**. **Cincinnati** and **Turco** incisions may be used.
- Limited soft tissue release
 - ▶ For **equinus** alone - posterior release
 - ▶ For **adduction** alone - medial release
 - ▶ For **cavus** alone - plantar release
- **Dillwyn Evans** procedure: thorough soft tissue release (PMSTR) for neglected CTEV in children aged 4-8 years.
- **Tendon transfers** - min. age is **5 years**; **tibialis anterior** is transferred to the outer side of the foot.
- Done after **14 years age** in **skeletally mature foot**.
- **Triple arthrodesis** involves fusion of the three joints of foot - **subtalar** (talo-calcaneal), **calcaneo-cuboid** and **talo-navicular** joints (**most difficult**).
- **Dwyer's osteotomy**; open wedge osteotomy of calcaneum to correct varus of the heel.
- Maintenance of correction: CTEV shoes and splints; **Dennis Browne** splint.

Screening Tests for CTEV

- Dorsiflexion test**
 - ▶ Normally, the foot of a newborn child can be dorsiflexed until the dorsum touches the anterior aspect of the shin of the tibia
 - ▶ In CTEV this is not possible
- Plumblin test**
 - ▶ Line drawn from centre of the patella to tibial tubercle when extended down should cut through it and 2nd metatarsal normally
 - ▶ In CTEV with medial rotation of tibia, it cuts through fourth or fifth intermetatarsal space
- Scratch test**
 - ▶ Scratch over the medial sole everts the foot (tests for peroneals)
 - ▶ Scratch over the lateral sole inverts the foot (tests for invertors)



Fig. 20.39: Clinical photograph of bilateral clubfoot seen from the front

Coxa Vara

- This is a term used to describe a hip in which the **angle between the neck and the shaft of femur is less than the normal 125°**.
- Noticed as a **painless limp** in a child who has just started walking.
- O/E, **abduction and internal rotation of the hip are limited** and the **leg is short**.
- Epiphyseal plate may be too vertical.
- **Trendelenburg's sign is positive** (in coxa valga also); **NO** telescoping.
- There may be a separate triangle of bone in the inferior portion of the metaphysis (**Fairbank's triangle**).
- Treatment is by **subtrochanteric corrective osteotomy**.

Slipped Capital Femoral Epiphysis

- MC affects **boys** aged **10-16 years**; 30% are bilateral; a/w **obesity** (may be **endocrine** abnormality).
- **Pain in the groin**, **limitation of internal rotation and abduction**; **Trendelenburg's sign may be positive**.
- X-ray, CT and MRI are useful; Ultrasound is **NOT** useful.

- **Trethowan's sign**: A line drawn along the lateral edge of femoral neck (**Klein line**) passes superior to the head unlike in a normal head where it passes bisecting the head.
- **Capener's sign**: Normally, the posterior acetabular margin cuts across the medial corner of the metaphysis. But in slipped epiphysis the entire metaphysis remains lateral to the posterior acetabular margin.
- Treatment is mainly **operative internal fixation** to avoid avascular necrosis.

More Congenital Malformations

Trunk and Spine

- Klippel-Feil syn** **Congenital fusion of cervical vertebrae**, short neck, low posterior hairline, and painless limitation of cervical movements. '**Mirror movements**' may occur.
- Sprengel's shoulder** **Congenital high scapula**; there is a failure of descent of the scapula. In some cases a bar of bone, the **omovertebral bar**, tethers the scapula to the spine. Associations include **congenital scoliosis** with **hemivertebrae**, **Klippel Feil syndrome**, **absent/fused ribs**, **diastomatomyelia**, **renal abnormalities**, **spina bifida**, **synringomyelia**, **platybasia** and **situs inversus**.
- Hemivertebra** Growth of only one half of a vertebra resulting in scoliosis, common in **dorsal spine**
- Block vertebra** Bodies of two vertebra are joined together with no intervening disc space, common in **cervical spine**.
- Diastematomyelia** A longitudinal **fibrous or bony septum** dividing the spinal canal into two
- Congenital torticollis** It is characterized by contracture of the **sternocleidomastoid** muscle
- Diaphyseal aclasis** **Congenital**; AD; multiple exostoses; misnomer since exostoses arise from the **metaphysis** and point away from the joint.

Upper limb

- Phocomelia** Lack of development of part of limb, distal part being present (seal limbs); seen in newborns with **thalidomide** (as a sedative) use in pregnant ladies
- Absence of radius** The hand deviates to lateral side because of lack of normal support to the radius (**radial club hand or manus valgus**).
- Congenital radioulnar synostosis** The forearm bones are joined together proximally, thus preventing forearm pronation and supination

Contd...

Madelung's deformity	Defective growth of the distal radial epiphysis resulting in deformity of the distal radius, and dislocation of the head of the ulna dorsally. Seen in Turner's syn.
Madelung collar	In type 1 multiple symmetric lipomatosis, lipomas in the neck region giving a bull-neck appearance.
Syndactyly	Webbing of two or more fingers, MC being ring and middle fingers ; simple when only soft tissue involved, complex when bone is also involved.
Camptodactyly	It is nontraumatic flexion deformity of the fingers at the proximal interphalangeal joint.
Clinodactyly	It is a curvature of digit in the radioulnar direction in contrast to camptodactyly where the curvature is in the anteroposterior direction.
Kirner's deformity	It is a deformity of the little finger in which there is radial and palmar curving of the distal phalanx.
Lower limb	
Rocker bottom foot	Congenital vertical talus ; seen in Turner's syndrome
Pobble foot	Hypoplasia of the toes
Pseudoarthrosis of the tibia	A birth defect in the lower third of the tibia in children whereby a fracture in this region fails to unite. May be associated with neurofibromatosis or fibrous dysplasia .

Osteogenesis Imperfecta

- Also called **brittle bone** disease and **Lobstein syndrome; AD**
- Defect is in synthesis and deposition of **type 1 collagen**.
- Multiple fractures due to trivial trauma with **Wormian** bones is seen.
- Out of the 8 types (type I-VIII); Type I is the mildest form and type II is the most severe.
- Clinical features: **Blue sclerae**, **short stature**, **hearing loss**, **respiratory** problems, and dentinogenesis imperfecta.
- '**Shish kebab**' technique is a complex surgical procedure used for correction of severe long **bone defects in osteogenesis imperfecta**.

ARTHRITIDES

Osteoarthritis

- Degenerative non-inflammatory** joint disease
- Risk factors: **Age > 55 years**, **obesity**, **repetitive joint stress** (heavy manual labor, athletes)

- Types: **Primary OA (Idiopathic)** is MC than secondary OA (trauma, metabolic disorder, inflammatory arthropathy)
- Pathology/X-ray:
 - **Fibrillation** and **degeneration of articular cartilage**
 - **Eburnation** and formation of **joint mice/loose bodies**.
 - **Subchondral sclerosis/subchondral cysts/geode**
 - **Osteophyte formation/growth of surrounding bone**
 - Joint space **narrowing**.
- Clinical:** Joint **crepitus**, **pain** (**bone pain** since cartilage has no nerves) **along joint line** which **worsens with exercise** and **weight bearing** and improves with rest.
- Quadriceps** (vastus medialis) weakness/atrophy is a/w knee OA
- X-ray for knee:** **Bilateral weight-bearing 45-degree bent knee posteroanterior, lateral, and patellofemoral joint views (Merchant view)**
- Treatment:** **Weight loss**, **NSAIDs**, **corticosteroid joint injections**, **joint replacement**; **Capsaicin** cream, which depletes local sensory nerve endings of **substance P**, when applied topically can reduce knee and hand pain without NSAIDs.

Commonly affected joints

- **Weight bearing joints:** MC affects **Knee; Hip, Cervical and lumbosacral spine, and first metatarsophalangeal joint**.
- **Finer grip joints:** **Small joints of hands: Distal interphalangeal joints (DIP - Heberden's)** more common than **proximal interphalangeal joints (PIP - Bouchard's nodes)** and the base of the thumb.

EXTRA EDGE

- **Spared joints in OA:** **Wrist, elbow, ankle; Ankles**, may be spared because their articular cartilage may be uniquely resistant to loading stresses.
- **Acetaminophen (paracetamol)** is the initial analgesic of choice for patients with OA in knees, hips, or hands (Harrison, 19th/2231).

Other Arthritis

- Rheumatoid arthritis: See **connective tissue diseases** under 'systems'.
- Psoriatic arthritis: See **dermatology** chapter (Pg 1044, 1165).
- Juvenile Rheumatoid Arthritis (**JRA**): In children; fever, rash, iridocyclitis, pericarditis and **negative RF**.
- Felty's syndrome:** **RA + hypersplenism** due to lymphocyte infiltration.

Gout

- **Asymmetric** joint distribution; joint is **swollen, red and painful**.
- Classically - painful **MTP joint of big toe (podagra)**.
- **Tophus formation** (often on external ear or Achilles tendon). Acute attack tends to occur **after alcohol consumption** or a **large meal**.
- Precipitation of **monosodium urate crystals** into joints due to **hyperuricemia**, which can be caused by Lesch Nyhan syndrome, **PRPP excess**, ↓ excretion of uric acid (e.g. **Thiazide diuretics**), ↑ cell turnover (cancer chemotherapy) or von Gierke's disease. Crystals are **needle shaped negatively birefringent**. More common in men.
- X-ray: Bone erosions with **overhanging sclerotic margins - Martel's sign** or **G-sign**; Chronic gout shows '**punched out**' lesions.
- Treatment: **Allopurinol, probenecid, colchicine**, NSAIDs.
- Radiography is the main imaging modality for detecting the progression of gout, but there is a **5-10 years latent period** between first clinical symptoms and appearance of specific radiographic findings.

EXTRA EDGE

- **Pseudogout:** Deposition of **calcium pyrophosphate crystals** within joint space; forms **basophilic, rhomboid crystals** that are **weakly positively birefringent**; usually affects large joints (classically **knee**); > 50 years old. No treatment a/w **periarticular soft tissue calcification**.

BONE INFECTIONS

Acute Osteomyelitis (OM)

- **MC OM in children: Primary (hematogenous)**
- **MC OM in adults: Secondary**; due to contiguous focus of infection (following open # or bone operation)
- **MC type** of OM: **Secondary** (accounts for 80% cases)
- **MC cause** of OM: **S aureus**; (in neonates and infants **Streptococcus** is the second MC cause).
- **MC cause** of OM in **sickle cell disease: Salmonella**.
- **MC site** in **children: Lower femoral** epiphysis
- **MC site** in **adults** and **IV drug abusers: vertebrae**
- **MC complication** of acute OM: **Chronic OM**

Clinically

- Acute hematogenous osteomyelitis starts in the metaphysis.
- Fever, swelling of limb, acute pain, **toxic child**.
- ESR (> 100 mm/hr)** and **CRP are elevated**.

Radiology of Acute OM

- Early X-ray within 24 hours is normal.

- **Earliest X-ray sign = loss of soft tissue planes** (by 24-48 hours).
- **Earliest bony sign on X-ray** = periosteal new bone formation (**periosteal reaction**).
- **Radiographic latent period** (earliest time by which X-ray changes appear) for acute osteomyelitis in **extremities is 8-10 days** and in **spine is 21 days**.
- **MRI** shows **marrow edema** beginning in **6 hours** and is the **imaging investigation of choice**.
- **99mTc bone scan is the second best** radiological investigation.
- **Ultrasound** is valuable for identifying **pus collection**.

Treatment

- **Criteria** for diagnosis of osteomyelitis: **Morey and Peterson's** criteria and **Peltola and Valvenen's** criteria.
- If seen < 48 hours, broad spectrum antibiotic for **6 weeks**; if > 48 hours surgical exploration and drainage required and antibiotics for **6 weeks**.

Complications

- **Chronic OM** (MC complication)
- Septicemia
- Acute pyogenic arthritis
- Pathological fracture
- Growth plate disturbances.

Chronic Osteomyelitis

- **Chronic discharging sinus** is the MC presenting symptom - MC cause of **non-healing sinus** is the sequestrum.
- **Lower end of femur** is MC site.
- MC due to delayed and inadequate treatment of acute OM.
- X-ray show - **Sequestrum** (a piece of dead bone, surrounded by infected granulation tissue trying to 'eat' the sequestrum away) and **involucrum** (the dense sclerotic bone overlying a sequestrum); **cloacae** are **holes in the involucrum** for pus to drain out.
- **Surgery** is the treatment of choice. After surgery a **continuous suction irrigation system** to wash out the marrow cavity with antibiotics and detergent is used for 4-7 days.
- **Complications** of chronic OM: Suppurative arthritis; metastatic infection/abscess; growth abnormalities; pathological fracture; soft tissue contracture; amyloidosis.

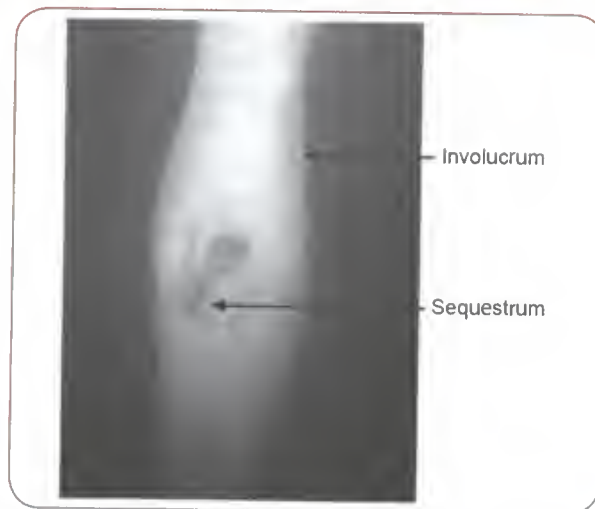


Fig. 20.40: Sequestrum and the involucrum

Sequestra

- **Ring** sequestrum: Amputation stumps and around pin tracks
- **Tubular** sequestrum: Hematogenous OM; segmental fractures
- **Black** sequestrum: Acinomycolosis
- **Ivory** sequestrum: Syphilis
- **Granular** sequestrum: Salmonella
- **Rice grain/sandy/feathery** sequestrum: TB.

Other Special Types of Osteomyelitis

Garre's OM A type of **chronic OM; sclerosing, non-suppurative**, NO discharging sinus, differentiate from Ewing's sarcoma or osteosarcoma.

Brodie's abscess Special type of **chronic OM** where the body defense mechanisms have been able to contain the infection so as to create a **chronic bone abscess** containing pus or jelly like **granulation tissue** surrounded by a zone of sclerosis—seen on **X-ray as a oval/circular lucent area surrounded by a zone of sclerosis**; MC in **lower end of tibia**.

Salmonella OM MC in children with **sickle cell anemia**; occurs during convalescent phase after acute attack of typhoid fever; subacute type of OM; X-ray shows **diaphyseal sclerosis**.

Septic Arthritis

- A true orthopedic **emergency**.
- **Hematogenous** route of infection is MC.
- **MC joint** affected is **knee** (position is flexion)
- MC causative organism is **S aureus**.

- Diagnosis is by synovial fluid analysis by joint aspiration - **WBC counts** > 1 lakh/mL and synovial fluid glucose is 30% that of serum levels.
- Treatment is **surgical** - By arthrotomy (opening joint capsule) and surgical drainage of pus (decompression), synovectomy and antibiotics (2 weeks IV and 4 weeks oral).
- Septic arthritis results in bony ankylosis and is the MC cause of **bony ankylosis**.

Tom Smith Arthritis

- **Septic arthritis of hip in infancy** which may completely destroy the cartilaginous femoral head (**chondrolysis**).
- **Hip joint classical position is flexion, adduction, external rotation** (a position that maximizes capsular volume and stretching due to effusion is minimal).
- When child presents later after 1 month—there will be limp; unstable gait, shortening of limb, telescopic and hypermobile joint (increased movements in all directions).

Transient (Toxic) Synovitis of Hip

- MC cause of **acute hip pain** in children **aged 3-10 years**.
- The disease causes **arthralgia** and **arthritis** secondary to a transient inflammation of the synovium of the hip.
- MC in boys, MC unilateral, a/w recent h/o URTI.
- **Hip joint is held in classical position is flexion, adduction, external rotation**
- **WBC count, ESR and CRP** are within normal limits.
- Treat with bed rest, non-weight bearing and NSAIDs.

Musculoskeletal (Bone and Joint) TB

- Skeletal TB is 3rd MC type of TB after lungs and lymph nodes; it is **always secondary to some primary focus** (lungs, lymph nodes, etc.)
- **Fibrous ankylosis** is a common outcome of healed TB of joints **except in the spine** where bony ankylosis is more common.

- Unlike pyogenic arthritis; **TB arthritis causes slow destruction**.
- Unlike pulmonary TB; systemic symptoms like fever, loss of appetite, weight loss are rare in skeletal TB.
- In TB arthritis: unlike other causes of joint space reduction (like OA, septic arthritis) which show subchondral sclerosis, in **TB arthritis – reduction of joint space, erosion of articular surfaces and periarticular rarefaction occur**.

Sites of Musculoskeletal TB

Disease	Notes
	Bone
Long bone: TB	<ul style="list-style-type: none"> • Tibia commonly affected • Lots of lytic lesions
osteomyelitis	<ul style="list-style-type: none"> • Minimal new bone formation unlike pyogenic osteomyelitis • Thin watery discharge • Multiple sinuses
Short bone (phalanges)	<ul style="list-style-type: none"> • TB dactylitis; Also called spina ventosa
Spine: TB spondylitis	<ul style="list-style-type: none"> • Also called Pott's disease • Spine is MC site of skeletal TB; MC involved is dorso-lumbar spine • Bacilli reach spine through paravertebral (Batson's) plexus • TB spine starts in vertebral body - Paradiscal type is MC; occasionally central body, pedicle, lamina and spinous process may be involved • Infection starts in the intervertebral disc • MC symptom is back pain; Tenderness, i.e. earliest sign • On X-ray - reduction of disc space is earliest sign; characteristic of TB spine is obliteration of disk space with destruction of two adjacent vertebrae • Anterior type of vertebral TB may show erosion of anterior part of the vertebral body, much the same as that in aneurysm of aorta – aneurysmal sign • TB spine with neurological involvement is Pott's paraplegia – MC involved is thoracic spine • First sign of spinal cord compression is Increased deep tendon reflexes and extensor plantar reflex • MRI is Inv. of choice for Pott's spine • Sequel of TB spine is bony ankylosis (remember 'spine is solid and solid is bony') • TB is the MC cause of kyphosis in males • Prof Rajasekaran has described radiographic signs of spine at risk • Treatment: ATT; When surgery is indicated for Pott's paraplegia, ATT + anterior/anterolateral decompression is done • Hong Kong operation is also done for Pott's spine.

	Joints
TB arthritis hip	<ul style="list-style-type: none"> • Hip joint is the joint MC commonly affected; MC in children/adolescents • Pain referred to knee severe at night (night cries); true shortening of lower limb present • Thomas test used to detect fixed flexion deformity of hip • 'Wandering acetabulum' may be seen • Stage 1 - stage of synovitis - stage of apparent lengthening • Stage 2 - stage of arthritis - stage of apparent shortening • Stage 3 - stage of erosion - stage of true shortening • ATT + girdlestone arthroplasty is done • Sequel is fibrous ankylosis
TB arthritis shoulder	<ul style="list-style-type: none"> • Shoulder joint TB may not produce any pus/cold abscess – 'Caries sicca' - meaning 'dry' or 'no effusion' • TB with polyarthritis is called Poncet's disease

Contd...

Contd...

- TB synovitis (Synovial TB)**
- **Knee joint** commonly affected; *begins in synovium*
 - Long standing TB knee causes **triple subluxation** (flexion of knee, posterior subluxation and external rotation of tibia)
 - **TRIPLE** subluxation is seen in TB, Rheumatoid arthritis; Ilotibial band contracture; Polio, Hemophiliac arthropathy (Low clotting).
 - **X-ray** essentially **normal**
 - Sequel is fibrous ankylosis

Tendon

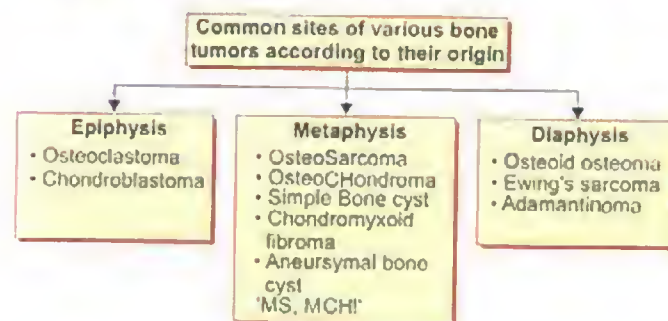
- TB tenosynovitis** **Compound palmar ganglion** (of flexor tendons at wrist)
- '**Melon seed badles**' are seen

Bursa

- TB Bursitis** Trochanteric bursitis

EXTRA EDGE

- Vertebral body involvement and disk space collapse is typical of **TB/infection**; WHEREAS malignancy involves posterior elements (pedicle, lamina, spinous process) and disk space preserved in **metastatic disease**.

BONE TUMORS**Usual Sites of Certain Bone Tumors****Enneking Classification****Benign musculoskeletal tumors**

- **Stage 1 - Latent** - Lesions are intracapsular and asymptomatic; grow slowly and stop; X-ray—well defined margin with **thick** rim of reactive bone; no cortical destruction or bone expansion. Usually asymptomatic and do not require treatment (e.g. small non-ossifying fibroma)
- **Stage 2 - Active** - Lesions are intracapsular but actively growing. X-ray—well defined margin with **only thin** rim of reactive bone. Treatment consists of extended curettage (e.g. aneurysmal bone cyst)
- **Stage 3 - Aggressive** - Lesion is **extracapsular**. X-ray: Tumor has **broken through** reactive bone and possibly cortex. Treatment: Extended curettage and marginal or even wide resection (e.g. symptomatic osteoclastoma)

Malignant musculoskeletal tumors

- Stage I - Low grade
- Stage III - Metastases
- Stage IIIA - Intracompartmental
- Stage IIIB - Extracompartmental

Contd...

Contd...

Benign bone forming tumors

- Osteoblastoma** • Same as osteoid osteoma but larger and found in vertebrae
- Osteoclastoma** • Affects **20-40 years** age group
- Affects **epiphysis** of long bones – lower femur, upper tibia
 - **Soap bubble appearance** on X-ray
 - **spindle shaped cells** (mononuclear stromal cells) with multinucleate giant cells in fibrous stroma seen; excision of tumor + reconstruction required

Benign Cartilage forming tumors

- Osteochondroma (exostoses)** • **MC benign** bone tumor
- Commonly originates from **metaphyses** of long bones, flat bones and small bones of hand and feet
 - Grows rapidly during childhood (period of most rapid skeletal growth)
 - Mature bone with **cartilaginous cap** seen
 - Multiple hereditary exostoses - **diaphyseal aclasis** - autosomal dominant - has **more chances** of malignant transformation
 - Rare malignant transformation to chondrosarcoma - indicated by **increase in thickness of cartilage cap, increase in pain and size after skeletal maturity**
- Enchondroma** • Affects **small bones of hands, feet**; arises from remnants of epiphyseal cartilage
- **Ollier's disease** – nonfamilial multiple enchondromas
 - **Maffucci's syndrome** – familial multiple enchondromas with cavernous hemangiomas of skin and soft tissues
 - Both above syndromes are a/w ovarian malignancy and cerebral gliomas
- Chondroblastoma** • Aka **Cadman** tumor
- Arise in **epiphysis** of long bones
 - Affect males < 20 years
 - Calcium deposition surrounding the chondroblasts, which are typically polyhedral shape, results in typical '**chicken-wire calcification**'

Malignant bone forming tumors

- OsteoSarcoma** • **Second MC** primary malignant bone tumor (after **multiple myeloma**, which is **THE MC** primary malignant bone tumor)
- Peak at **15-25 years**
 - **Predisposing factors** – **Paget's disease** (adult osteosarcoma), familial **retinoblastoma**, **bone infarcts**, **radiotherapy**, **fibrous dysplasia**, **enchondroma**
 - Affects **Metaphysis** of long bones, **lower femur**, **upper tibia** (knee)
 - Present with **pain and swelling of few weeks to months**; **egg-shell cracking with pulsations** suggest osteosarcoma
 - It is an **osteoid matrix forming** tumor
 - X-ray – **lytic lesion with moth eaten** appearance, spiculated **periosteal reaction**; **Sunray** or **Sunburst appearance** (due to calcification along blood vessels); cuff of periosteal new bone formation at margin of soft tissue mass – **Codman's triangle**, new bone formation; **↑ ALP**
 - Pre-op chemotherapy with limb sparing surgery with post-op chemotherapy is standard
 - **Extremely radioresistant**; **poor prognosis**
 - **Rasen T-10 protocol**: high doses of Methotrexate, Doxorubicin, Cisplatin and a combination of bleomycin, cyclophosphamide and dactinomycin
 - **Hematogenous metastases** occur to the **lung or bone**; mets to the same or immediately adjacent bone is called **skip lesion**
 - **Parosteal osteosarcoma** originates in **periosteum** and grows outside the bone; must be distinguished from **myositis ossificans** (clear cleft separates this from the bone).
- Ewing's sarcoma** • **2nd decade MC** affected; MC in **boys**; typically arising from **medullary cavity** with invasion of Haversian system.
- Presents with **large soft tissue** component **without osteoid matrix**, and typical '**onion skin**' periosteal reaction. (Note: Codman's triangle may **also** be seen in Ewing's sarcoma).
 - Ewing's will stain positive for **PAS (cytoplasmic glycogen)** and will have a positive vimentin stain; antibodies to **CD99** are found on the cell surface in ewing's
 - It affects **diaphysis** of long bones (**MC femur**), flat bones;
 - MC symptoms is **pain**; swelling; **fever**; raised ESR

Contd

Contd.

Benign bone forming tumors

- Anaplastic small blue round cell malignant tumor (PNET= primitive neuroectodermal tumor); chromosome **11:22 translocation**; expresses p30/32 **MIC2** antigen;
- It is **extremely aggressive with early mets**, but **responds well to chemotherapy** – curable tumor esp. in children < 11 years;
- t(11:22) corresponds to **EWS/FLI** gene fusion—seen in 85% of patients.

Malignant cartilage forming tumor**Chondrosarcoma**

- Affects men 30-60 years;
- Affects flat bones and long bones;
- May be primary or arise from osteochondroma;
- Presents with **pain and swelling**;
- X-ray—**expansile glistening mass within medullary cavity, mottled calcification** within tumor; treat with local ablation

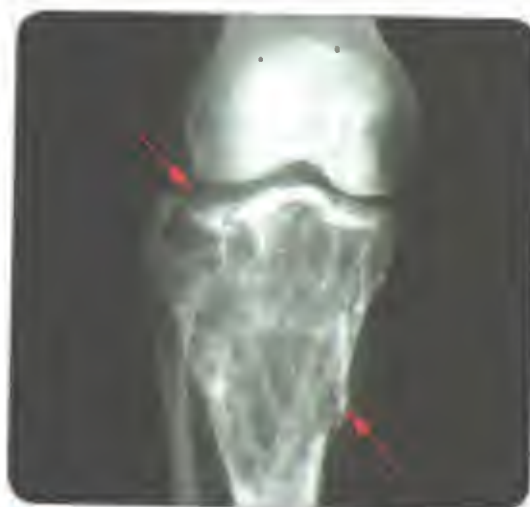
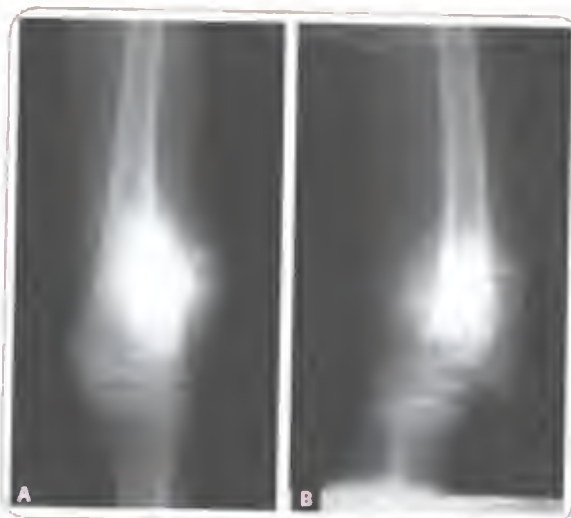


Fig. 20.41: A giant cell tumor arising from the upper end of tibia with multiple pathological fractures due to thinning of the cortex. Pathological fracture is a late feature of a giant cell tumor



Fig. 20.43: Ewing's sarcoma diaphyseal lesion with onion peel appearance



Figs 20.42A and B: Radiological features of osteosarcoma

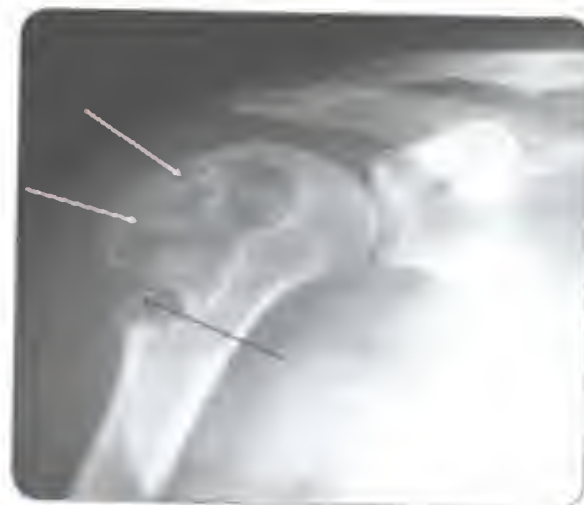


Fig. 20.44: Chondrosarcoma of proximal humerus showing lytic lesion with calcification (cotton wool appearance) lytic lesion (black arrow) speckled calcification (white arrows)

Uncommon Bone Tumors

- | | |
|-------------------------------------|--|
| Hemangioma of bone | <ul style="list-style-type: none"> • Benign tumor affecting vertebrae and skull • Young adults present with persisting backache • X-ray – loss of horizontal striations and prominence of vertical striations of the affected vertebral body • Treatment is radiotherapy |
| Ameloblastoma (Adamantinoma) | <ul style="list-style-type: none"> • 3rd to 5th decade of life • Common tumor of mandible (near third molar tooth); also occurs long bones - lower diaphysis of tibia. • X-ray – honeycomb appearance • Slow growing, locally malignant tumor • Treatment is by resection |
| Chordoma | <ul style="list-style-type: none"> • Locally malignant tumor supposedly originating from remnants of notochord • Only axial skeleton involved: Sacrococcygeal; spheno-occipital; vertebral body; clivus; cervical spine are common sites • Bone destruction is the only hallmark feature of this tumor |

D/D of Solitary Bone Lesion

Features	Simple (unicameral) bone cyst	Aneurysmal bone cyst	Fibrous dysplasia
Age	1st decade	2nd decade	20-30 years
Bones affected	Upper humerus	Tibia; posterior elements of vertebra (spinous process, transverse process and pedicle)	Proximal femur
Locations	Metaphysis; central	Metaphysis; eccentric	Metaphysis
X-ray	Radiolucent lesion in contact with growth plate, maximum width less than width of growth plate; 'fallen fragment sign'	Expansile (blood filled) lesion ballooning the bone, cyst may extend to soft tissues simulating malignant tumor	Multiloculated groundglass appearance, trabeculations ++, 'shepherd crook' deformity of proximal femur
Treatment	Curettage and bone graft; intralesional steroid injection; intralesional sclerosing agent injection	Curettage and bone graft	Curettage and bone graft

Non-neoplastic lesions simulating bone tumors

- Fibrous lesions (nonossifying fibroma, ossifying fibroma, fibrous dysplasia, cortical desmoids)
- Cystic lesions (unicameral bone cyst, aneurysmal bone cyst, ganglion cyst, epidermoid cyst)
- Bone island
- Bone infarct
- Paget's disease
- Brown tumor of hyperparathyroidism
- Osteomyelitis
- Stress fracture

MORE BONE DISORDERS**Osteoporosis**

- **Reduction of bone mass** in spite of normal bone mineralization. Sparse trabeculae.
- **Type I = Postmenopausal**; ↑ bone resorption due to ↓ estrogen levels.
- **Type II = Senile osteoporosis** - affects men and women > 70 years.
- **Vertebral crush fractures** - acute back pain, loss of height, kyphosis; **Distal radius (Colle's) fractures, vertebral wedge fractures**.
- Prophylaxis = **exercise; calcium; low dose estrogen therapy**.
- Levels of serum **calcium, phosphorus and alkaline phosphatase** are **normal**.
- Treatment:
 - Vitamin D and calcium
 - **Calcitonin—nasal spray** better than parenteral route; **reduces bone pain**.
 - **Selective estrogen receptor modulators—raloxifene** (REDUCES - risk of vertebral fractures, LDL, breast cancer risk; INCREASES - hot flashes; thromboembolism; NO EFFECT - on vaginal dryness).
 - **Teriparatide** - an analog of PTH; it **stimulates the production of new collagenous bone matrix** that must be mineralized (so supplement sufficient intake of vitamin D and calcium); contraindicated in **Paget's disease and osteosarcoma**; causes **hypercalcemia**.
 - **Denosumab** - a monoclonal antibody that inhibits the proliferation and maturation of preosteoclasts into mature osteoclast bone-resorbing cells. It does this by binding to the osteoclast receptor activator of nuclear factor kappa B ligand (RANKL).
 - Glucocorticoids are contraindicated.

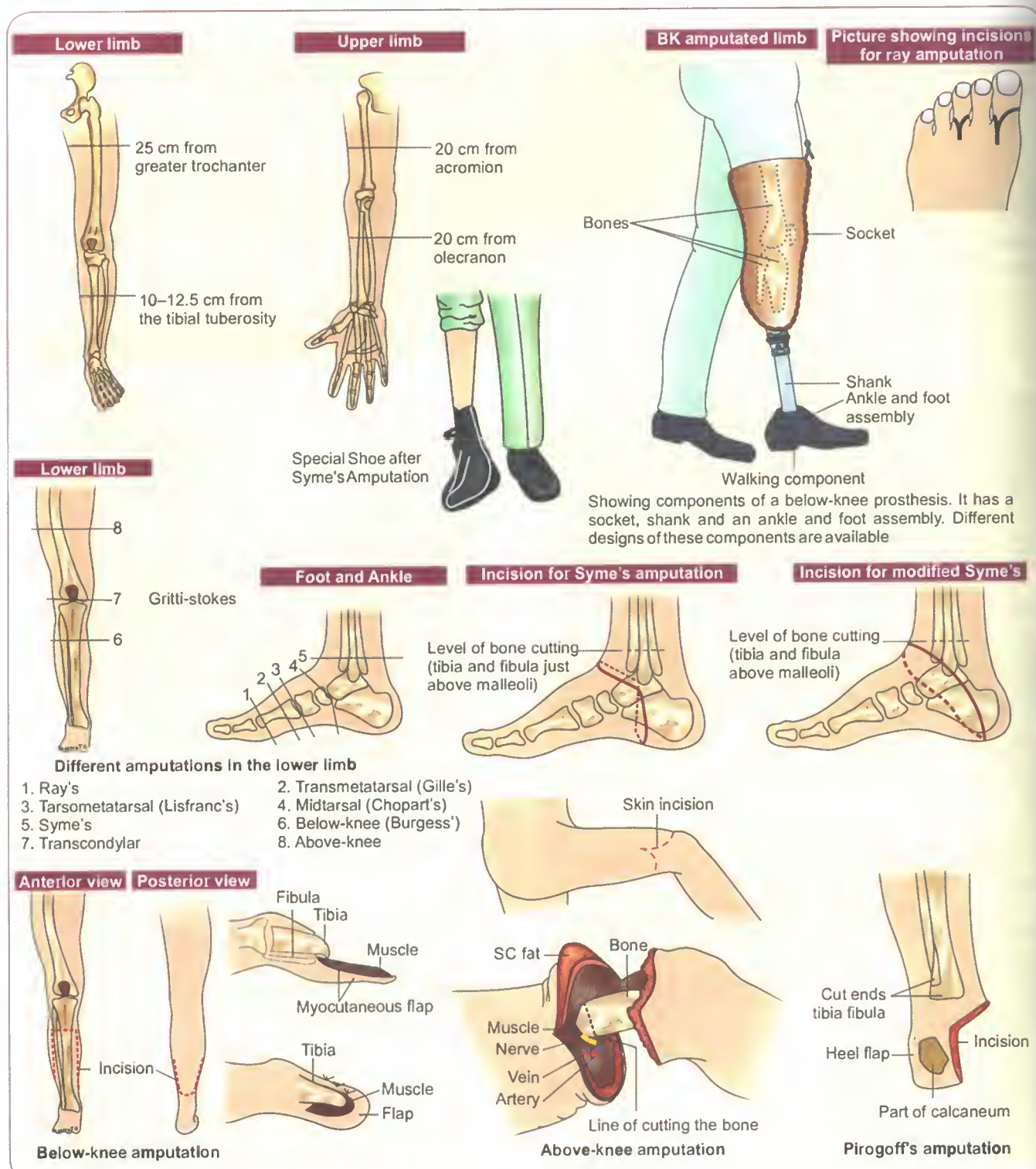


Fig. 20.45: Different types of amputations, their levels, the ideal length of the stump and some prosthesis.

Bisphosphonates

- MOA - **inhibit osteoclast induced bone resorption**
- Oral-alendronate** and **risedronate** (once weekly), **ibandronate** (once monthly) - all cause **erosive esophagitis**
- IV - pamidronate** (3-6 monthly once) and **zoledronic acid** (once yearly)
- Acute phase reaction** - fever, chills, flushing, muscle pain **MC with zoledronic acid**
- Jaw osteonecrosis** has occurred with high-dose therapy with **zoledronic acid or pamidronate** for patients with myeloma/osteolytic metastases
- Bisphosphonates can cause **atypical 'chalkstick' fractures** of the femur (**insufficiency fracture**) X-ray shows **lateral cortical fracture**
- There is also increased risk of developing **esophageal cancer**.

EXTRA EDGE

- Immobilization osteoporosis** - in stroke and **hemiplegic** patients. BMD changes are seen first in **proximal humerus**.
- Bone Mineral Density Score (**T score**): Hip bone density is most reliable in predicting risk of hip fracture and spine bone density is used to monitor response to treatment.

Normal bone	T-score > -1
Osteopenia	T-score between -1 and -2.5
Osteoporosis	T-score < -2.5.
Established (severe) osteoporosis	T-score < -2.5 + presence of a non-traumatic fracture

Paget's Disease (Osteitis Deformans)

- Abnormal bone architecture caused by ↑ in both osteoblastic and osteoclastic activity. Possibly viral in origin.
- Serum calcium, phosphorus and PTH levels are **normal**. ↑ **serum ALP (Alkaline Phosphatase)**. **Mosaic** bone pattern; long bone chalk-stick fractures.
- Age > 40y; M:F 2:1
- Pain** is the MC presenting symptom.

Skull

- Osteoporosis circumscripta** (outer table destroyed only)
- '**Cotton wool**' areas of sclerotic bone
- ↑ **Hat size!** (enlarged skull, BUT facial bones not commonly affected, cf. fibrous dysplasia) - **Tam O Shanter sign**
- Hearing loss** common due to auditory foramen narrowing.

Contd...

Contd...

Pelvis

- Cortical thickening
- Enlargement of pubis/ischium
- Coarse trabecular pattern
- '**Brim sign**'.

Spine

- Especially lumbar spine. Enlargement of vertebrae and coarsened trabeculae and cortical thickening produces the '**picture frame**' vertebral body.

Extremities

- Leading edge of the lytic phase of the disease has a '**Blade of grass**' appearance
- '**Banana fractures**' (incomplete pathologic fractures).

Complications:

- **Pathological fractures** (usually femur = '**Shepard's crook**' deformity)
- Sarcomatous change in **1%** (usually **osteosarcoma**).
- ↑ blood flow from ↑ arteriovenous shunts may cause high output **CHF**
- **Calcific aortic stenosis** and diffuse vascular calcifications.
- Osteoclast-rich **benign giant cell tumors** may arise in areas adjacent to pagetic bone and respond to glucocorticoid therapy.
- **Hyperuricemia** and **urinary stones** may occur.
- Treatment: Bisphosphonates** are the drugs of choice.

Complex Regional Pain Syndrome (CRPS)

- CRPS type 1:** Also called **Reflex Sympathetic Dystrophy Syndrome**, **Sudeck's atrophy**; no demonstrable nerve lesion.
- Symptoms: **Burning, pain** and **swelling** of an extremity accompanied by signs of **trophic skin changes** in the extremity (e.g. skin atrophy, hyperhidrosis, brittle nails), **osteoporosis**, **vasospasm**.
- MC** occurs in the **hand (distal radius)** and is a/w ipsilateral restricted shoulder motion - **shoulder-hand syndrome** - common after neck or shoulder injuries or following myocardial infarction; swelling is diffuse ('**catcher's mitt hand**') and not restricted to joints.
- X-rays reveal severe generalized **osteopenia**.
- Bone scans** also show **increased uptake**.
- Treatment - Conservative: physiotherapy + alprazolam/diazepam; Surgical: sympathetic block (**stellate ganglion** or lumbar) or **sympathectomy**.
- ALSO KNOW:** CRPS type 2 = **causalgia**; a/w known nerve lesions.

Named 'BONE' Diseases

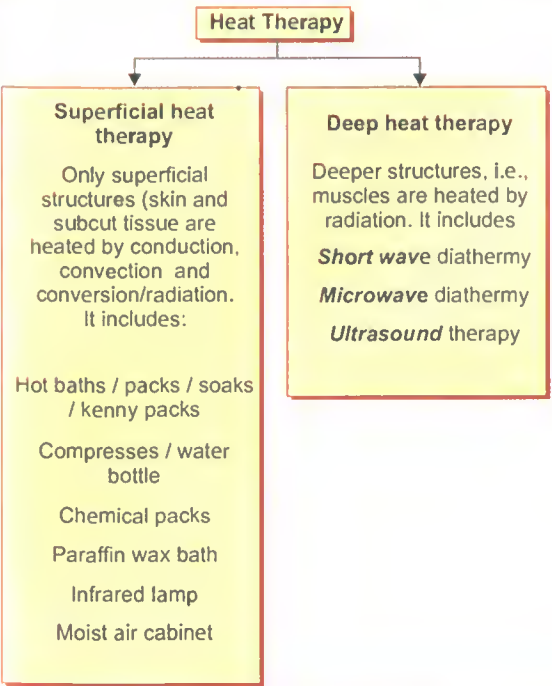
CAN dle bone disease	MEL orheostosis (CAN dle MEL ts !)
STR iped bone disease	Osteopathia STR ata
SPOT ted bone disease	Osteo PO ikilosis
Marble bone disease	Osteopetrosis
Osteitis deformans	Paget's disease

Gait

Gait	Pattern	Cause
High stepping gait or foot drop gait	Due to drop of the foot, leg is lifted more in order to get clearance. The first to touch the ground is the forefoot and not the heel	Common peroneal nerve palsy, sciatic nerve palsy
Quadriceps gait or hand knee gait	Person walks with hand on the knee to prevent the knee from buckling in a quadriceps deficient knee with flexion deformity	Polio
Scissor gait	Legs are crossed in front of each other while walking due to spasm of adductors of the hip	Cerebral palsy
Antalgic or painful gait	The time taken on the affected leg is decreased (stance phase duration is decreased). Body weight is shifted quickly to the normal leg	Painful condition of foot, knee, hip etc.
Stiff hip gait	Lifts the pelvis and swings it forward in one piece, no flexion at hip	TB hip, rheumatoid hip, Ankylosing spondylitis, septic arthritis at hip
Stiff knee gait	Leg is circumducted and brought forward in order to get clearance	TB knee, painful shift knee
Trendelenburg gait or gluteus medius gait	Body swings to the affected side every time weight is borne on that side	Dislocated hip, CDH, congenital coxa vara, fracture neck of femur, gluteus medius paralysis
Gluteus maximus gait	Body swings backwards every time the weight is borne	Gluteus maximus paralysis in polio, anterior polio
Short limb gait	Becomes apparent only if limb shorter than 2 inches	Congenital short femur, shortening secondary to fracture
Frontal gait disorder	Difficulty with gait initiation - ' slipping clutch ' syndrome	Frontal subcortical small vessel disease
Calcaneus gait	No pushoff	Calf weakness
Hysterical gait		Seen in conversion hysteria

Gait Cycle

- Stance phase = 60%
- Heel strike → Mid stance → Push off
- Swing phase = 40%
- Acceleration → Mid swing → Deceleration
- **Rolling or Waddling gait:** Seen with proximal muscle weakness.
- **'Like a drunken sailor' gait:** Broad based gait seen in cerebellar ataxia (vermis lesions).



HIGH YIELD POINTS

- **Buckle #s in children** are incomplete #s that occur in metaphysis of bones adjacent to, but not involving the growth plate. Common site is distal radius. Treat by cast immobilization.
- In **treatment of Chronic osteomyelitis**, Tetracycline bone labelling and intraoperative use of Wood's lamp may aid in identification of devascularized bone. Well vascularized bone incorporates tetracycline which fluoresces under Wood's lamp.
- **Coventry osteotomy**—The weight-bearing axis of the body is transferred to the more normal lateral condyle of the knee—Standard procedure for early degenerative disease in elderly and middle-aged patients.

- **Ankylosing spondylitis**- Fecal carriage of *Klebsiella* is increased and this is related to exacerbations.
- **Osteosarcoma presents with pain first** and swelling later on. Bone to bone metastases are seen in Ewing sarcoma > osteosarcoma.
- MC congenital abnormality of foot is *Metatarsus adductus*.
- MC congenital anomaly of the hand is *Syndactyly*.
- **Pollicization** is an operation to shorten and rotate the - usually- index finger to form a thumb.
- **Myodesis:** During an amputation, stabilization of the divided muscles is of utmost importance. Inadequate techniques resulting in weak, retracted muscles or skin that cannot tolerate the necessary pressures will obviously compromise stability. Applying the myodesis technique for distal muscle stabilization gives greater stability as it involves the direct suturing of muscle or tendon to bone. Myodesis is **not recommended for ischemic patients**. Instead, the surgeon will probably employ the technique of myoplasty.
- A **Morel Lavallée** lesion represents a **closed degloving injury** associated with severe trauma which then presents as a hemolymphatic mass. The lesions classically occur over the greater trochanter of the femur.
- Surgery in a case of rickets is done after **growth plate healing** becomes normal.
- Avulsion of **anterior-inferior iliac spine** on X-ray is diagnostic of **rectus femoris** rupture.
- The **Piano Key test** can be used to assess for an **unstable DRUJ (Distal RadioUlnar Joint)**.
- **Ulnar Fovea sign** is used for injuries to the TFCC (Triangular fibrocartilage complex).
- The **Ulnocarpal Stress test (Nakamura test)** is a provocative test for ulnocarpal abutment syndrome (degenerative injury to the TFCC).
- Earliest changes of **Perthe's disease** can be best detected by **MRI**.

Author's Note

- As we all know, the subject "Medicine" includes aspects of all the subjects studied in the preclinical and paraclinical years of MBBS. Hence you will find a lot of overlap between these subjects and medicine—especially when preparing for PG Medical Entrance Exams. In fact, I always tell the PG aspirants that if they have finished the pre- and paraclinical subjects, then there is not much to fear about medicine. In this edition, I have reorganized the "medicine" chapter to make it more reader-friendly. Of course the system-wise presentation of the previous editions "Systems" still remains.
- Predominantly "medical" systems, viz. Cardiovascular system, Central nervous system, Respiratory system and Connective tissue disorders have been discussed entirely in this "medicine" chapter.
- For systems which have significantly both "surgery" + "medicine" aspects, viz. Renal system, Gastrointestinal system, Liver and Pancreas and Endocrine system—the "medical" part is discussed in detail in this "medicine" chapter whereas "surgical" parts have been discussed in "surgery" chapter—again system-wise.
- Also, here you will find the "systemic pathology" aspects of various systems along with the respective disorders. (Ex: Pathology of glomerular diseases under nephritic/nephrotic syndromes; pathology of myocardial infarction under Acute MI; pathology of Crohn's and Ulcerative colitis under inflammatory bowel disease etc.).
- The drugs corresponding to various systems have been dealt with in detail in Pharmacology chapter. For those wishing to read the drugs also along with the respective diseases, the page numbers of corresponding pages in pharmacology chapter have been mentioned.
- Similarly any links to the Radiodiagnosis chapter have also been mentioned in the respective areas.

CARDIOVASCULAR SYSTEM

PULSES

Jugular Venous Pulse (JVP)

- The **right internal jugular vein** is the best vein for accurate estimation of the central venous pressure.
- Recording of jugular venous pulse is called **phlebogram**.
- The waves in the normal JVP are as below:

a wave	Atrial contraction
c wave	Bulging of tricuspid valve into right atrium during right ventricular isovolumetric systole
v wave	Increasing volume of blood in the right atrium during ventricular systole as the tricuspid valve is closed
x descent	Atrial relaxation and downward displacement of tricuspid valve during ventricular systole
y descent	Opening of tricuspid valve and rapid inflow of blood into right ventricle

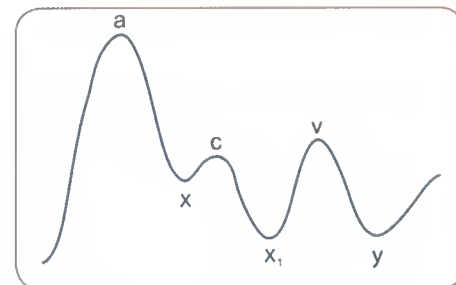


Fig. 21.1: Phlebogram

Abnormalities of JVP

Raised JVP with normal waveform	Fluid overload, right heart failure
Raised JVP with absent pulsation	SVC obstruction (edema of head and neck, collateral veins and absent venous pulsation)

Contd...

Contd...

Large (Giant) a wave	Tricuspid stenosis, pulmonary stenosis/hypertension, some cases of left ventricular hypertrophy (Bernheim effect)
Cannon a wave	Complete heart block, junctional rhythm, atrioventricular dissociation with ventricular tachycardia.
Absent a wave	Atrial fibrillation
Systolic (cv) waves	Tricuspid regurgitation, look for earlobe movement
Slow y descent	Tricuspid stenosis
Deep x and y descents	Constrictive pericarditis and pericardial tamponade

EXTRA EDGE

- The acoustic counterpart of a 'giant a wave'; is **right-sided/right ventricular S4** and its electrical counterpart is **P pulmonale**.
- 'Cannon a wave' is the hallmark of **atrioventricular dissociation**, i.e. the atrium are contracting against a closed tricuspid valve.

Kussmaul's Sign

- In BOTH **constrictive pericarditis** and **restrictive cardiomyopathy**, the JVP does not fall appropriately or may even increase during inspiration = **Kussmaul's sign**.
- Other causes of **Kussmaul's sign** are: **right ventricular myocardial infarction** and **severe right ventricular failure**.
- Kussmaul's sign is **ABSENT** in cardiac tamponade.

Arterial Pulse

Type of pulse	Seen in
Pulsus parvus et tardus	Aortic Stenosis (AS)
Pulsus alternans	Left ventricular failure (LVF)
Pulsus bisferiens	(Collapsing + slow rising) AR (with/without accompanying AS) Hypertrophic Obstructive Cardiomyopathy (HOCM)
Dirotic pulse	Has two palpable waves, one in systole and one in diastole. Seen in dilated cardiomyopathy (due to very low stroke volume)
Jerky pulses	HOCM Severe Mitral Regurgitation (MR) (when this develops rapidly) and in AR complicated by severe heart failure.

Contd...

Contd...

Type of pulse	Seen in
Collapsing ('Water Hammer') pulse	Aortic Regurgitation (AR) Patent Ductus Arteriosus (PDA) Ruptured sinus of valsalva or large AV communications Hyperdynamic circulation.
Pulsus paradoxus	(Pulse weakens in inspiration by more than the normal 10 mmHg) is caused by Cardiac tamponade Constrictive pericarditis Asthma Airway obstruction Superior vena cava obstruction.

HEART SOUNDS

Sound	Mechanism	Other features
S1	Due to mitral and tricuspid valve closure Occurs at onset of systole Loudest at mitral area	Loud S1 in hyperdynamic circulation (anemia, pregnancy, thyrotoxicosis), Mitral stenosis Soft S1 in heart failure, mitral regurgitation
S2	Due to aortic and pulmonary valve closure Occurs at end of systole Loudest at left sternal border	See below for detailed separate section about S2
S3	From ventricular wall due to abrupt cessation of rapid filling Occurs early in diastole Low pitched, often heard as 'gallop'	Maybe physiological in young people, pregnancy. Pathological in heart failure, mitral regurgitation
S4	Due to high atrial pressure Occurs at end of diastole	S4 = 'atrial kick' Always pathological – a/w severe LV hypertrophy (e.g. HOCM) Absent in atrial fibrillation.

Normal Second Heart Sound (S2)

- Has two components **A2** (aortic closure) and **P2** (pulmonary closure).

- During expiration A2 and P2 are superimposed – so single sound is heard
- During Inspiration A2 precedes P2—so splitting occurs.
- A2 is louder than P2 except in infants below 3–6 months.

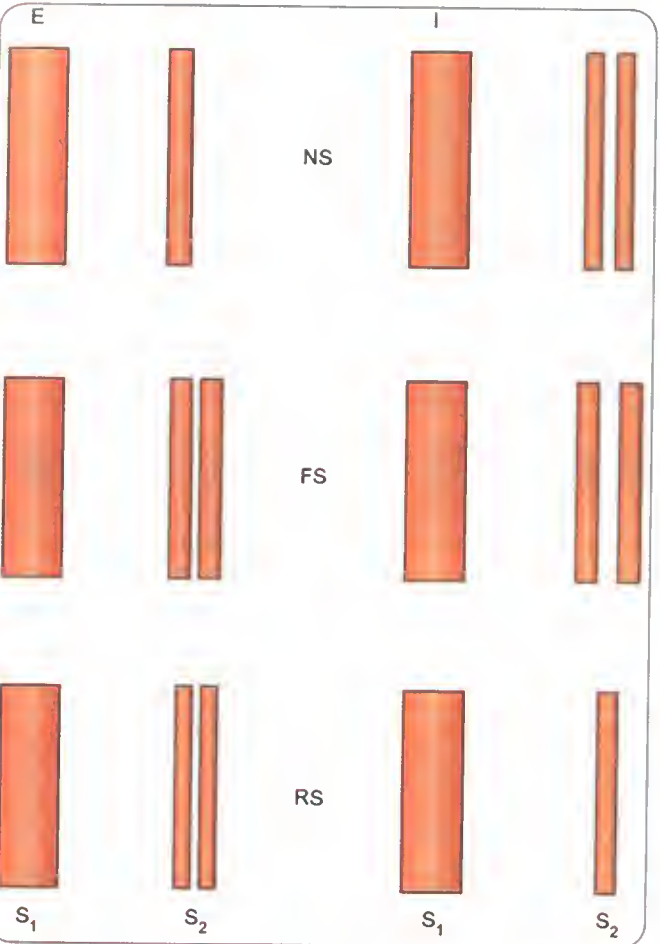
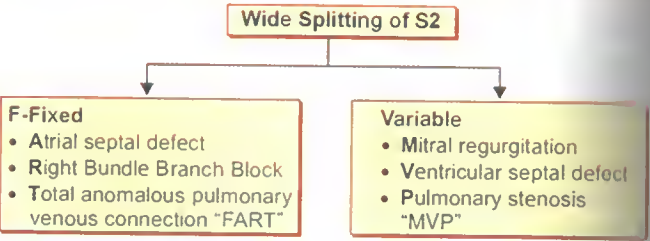


Fig. 21.2: Diagram showing splitting of second heart sound in the pulmonary area: E–expiration, I–inspiration, NS–normal split, FS–fixed split, RS–reversed split.

Abnormalities in Splitting of S2

- Normal S2 is single in expiration (i.e., A2-P2 interval < 0.03s) and A2-P2 interval > 0.03s in inspiration.
- **Wide splitting means** A2-P2 interval > 0.03s during expiration.
- **Wide variable splitting:** During inspiration the A2-P2 interval increases further.
- **Wide and fixed splitting:** The A2-P2 interval is the same in inspiration and expiration.
- **Reversed/paradoxical splitting** due to delayed left heart emptying (e.g. **LBBB, aortic stenosis**).



EXTRA EDGE

- **Widening of the S1** is due most often to **complete right bundle branch block** and the resulting delay in onset of the right ventricular pressure pulse.

HEART MURMURS

Basics

- **Systolic murmurs** begin with or after the first heart sound (S1) and terminate at or before the component (A2 or P2) of the second heart sound (S2) that corresponds to their site of origin (left or right, respectively).
- **Diastolic murmurs** begin with or after the associated component of S2 and end at or before the subsequent S1.
- **Continuous murmurs** are not confined to either phase of the cardiac cycle but instead begin in early systole and proceed through S2 into all or part of diastole.
- **Gallavardin effect:** The coarse systolic murmur of aortic stenosis (AS) may sound higher pitched and more acoustically pure at the apex.
- The **intensity of a heart murmur** is graded on a scale of 1–6 (or I–VI):
 - **Grade 1** murmur is very soft and is heard only with **great effort**.
 - **Grade 2** murmur is **easily heard** but not particularly loud.
 - **Grade 3** murmur is **loud** but is **NOT accompanied by a palpable thrill** over the site of maximal intensity.
 - **Grade 4** murmur is very loud and is accompanied by a **thrill**.
 - **Grade 5** murmur is loud enough to be heard with only the edge of the stethoscope touching the chest.
 - **Grade 6** murmur is loud enough to be heard with the stethoscope **slightly off the chest**.
- Murmurs of **grade 3 or greater intensity** usually signify important structural heart disease and indicate high blood flow velocity at the site of murmur production.

Systolic Murmurs

- **Early systolic:** Acute MR; TR; VSD
- **Mid-systolic:**
 - **Aortic:**
 - Obstructive: aortic stenosis (Supravalvular and valvular); coarctation of the aorta; aortic sclerosis
 - Subvalvular (discrete, tunnel or HOCM)
 - Increased flow, hyperkinetic states, AR, complete heart block
 - Dilation of ascending aorta, atheroma, aortitis
- **Pulmonary:**
 - Obstructive: pulmonary artery stenosis (Supravalvular and Valvular); Subvalvular (infundibular stenosis)
 - Increased flow, hyperkinetic states, left-to-right shunt (e.g. ASD)
 - Dilation of pulmonary artery
- **Late systolic:** MVP; TVP; acute myocardial ischemia
- **Holosystolic (PANsystolic):** MR, TR; VSD.

Diastolic Murmurs

- **Early Diastolic Murmurs:** AR, PR
- **Mid-Diastolic Murmurs**
 - Mitral stenosis
 - Carey-Coombs murmur (mid-diastolic apical murmur in acute rheumatic fever)
 - Increased flow across nonstenotic mitral valve (e.g. MR, VSD, PDA, high-output states, and complete heart block)
 - Tricuspid stenosis Increased flow across nonstenotic tricuspid valve (e.g. TR, ASD, and anomalous pulmonary venous return)
 - Left and right atrial tumors (myxoma)
 - Severe AR (Austin Flint murmur)

Continuous Murmurs

- Patent ductus arteriosus (PDA)
- Coronary AV fistula
- Ruptured sinus of Valsalva aneurysm
- Aortic septal defect
- Cervical venous hum
- Anomalous left coronary artery
- Proximal coronary artery stenosis
- Mammary souffle of pregnancy
- Pulmonary artery branch stenosis
- Bronchial collateral circulation
- Small (restrictive) ASD with MS
- Intercoastal AV fistula

Effects of Various Interventions on Systolic Murmurs

Intervention	HOCM	Aortic stenosis	Mitral regurgitation	Mitral valve prolapse
Squatting or handgrip	↑	↓ or ↔	↑	↓
Standing	↑	↑ or ↔	↓ or ↔	↑
Valsalva	↑	↓	↓ or ↔	↑
Exercise	↑	↑ or ↔	↓	↑
Amyl nitrite	↑	↑	↓	↑

Named Murmurs

Carvalho's murmur	▪ Early systolic murmur – In TR with normal pulm. artery pressure – In SABE in IV drug abusers
Graham Steele murmur	▪ Early diastolic murmur – in pulmonary incompetence
Carey-Coomb's murmur	▪ Short mid diastolic murmur; In acute mitral valvulitis, RF
Gibson's murmur	▪ Train in tunnel (continuous, machinery murmur) in PDA
Siegele's murmur	▪ In AR
Duroziez murmur	▪ In AR (over femoral artery)

EXTRA EDGE

- Usually **named murmurs** are **diastolic** except **Carvalho's** and **Still's murmur** (in children) are **systolic**.
- Venous hum at the root of the neck is also called "nun's murmur" and "bruit de diable" (the Devil's noise).

Triangle of auscultation

A space on the back where the relatively thin musculature allows for respiratory sounds to be heard more clearly with a stethoscope. It has the following boundaries:

- **Superiorly**, by the Trapezius
- **Inferiorly**, by the Latissimus dorsi
- **Laterally** by the medial margin of the scapula
- The **floor** is partly formed by the Rhomboideus major

ELECTROCARDIOGRAM (ECG)

Basics of ECG

- The **12 conventional ECG leads** record the difference in potential between electrodes placed on the surface of the body.

- These leads are divided into two groups:
 - 6 limb (extremity) leads and
 - 6 chest (precordial) leads.
- The limb leads record potentials transmitted onto the *frontal plane*, and the chest leads record potentials transmitted onto the *horizontal plane*.
- The six limb leads are further subdivided into:
 - 3 standard “bipolar” leads (I, II, and III) and
 - 3 augmented “unipolar” leads (aVR, aVL, and aVF).
- Each **standard bipolar lead** measures the difference in potential between electrodes at two extremities: lead I = left arm – right arm voltages, lead II = left leg – right arm, and lead III = left leg – left arm.
- The **augmented unipolar leads** measure the voltage (V) at one locus relative to an electrode (called the central terminal or indifferent electrode) that has approximately zero potential. The augmented leads are recordings between one limb and other two limbs.
- Thus, aVR = right arm, aVL = left arm, and aVF = left leg (foot).
- The lowercase *a* indicates that these unipolar potentials are electrically augmented by 50%.
- The **right leg electrode functions as a ground**:
 - The **six chest leads** are unipolar recordings obtained by electrodes in the following positions: lead V1, fourth intercostal space, just to the right of the sternum; lead V2, fourth intercostal space, just to the left of the sternum; lead V3, midway between V2 and V4; lead V4, midclavicular line, fifth intercostal space; lead V5, anterior axillary line, same level as V4; and lead V6, midaxillary line, same level as V4 and V5.
- **Einthoven’s triangle**: The 3 standard limb leads (I,II,III) form an equilateral triangle with the heart in the centre.

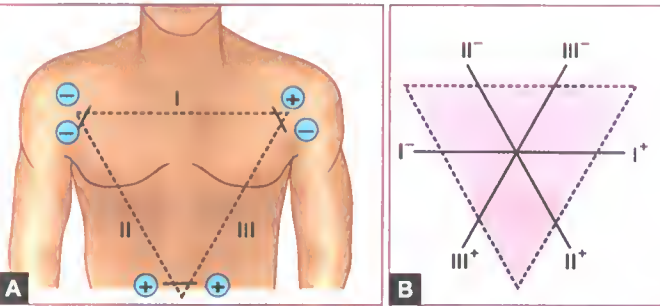


Fig. 21.3: (A) The Einthoven triangle of limb leads; (B) The triaxial reference system

Normal ECG

P wave	• Atrial depolarization
PR interval	• Conduction through AV node (< 0.2 s)
QRS complex	• Ventricular depolarization (< 0.12 s)
QT interval	• Mechanical contraction of ventricles
T wave	• Ventricular repolarization
ST segment	• Isoelectric ventricular contraction
U wave	Purkinje repolarisation; caused by hypokalemia, bradycardia

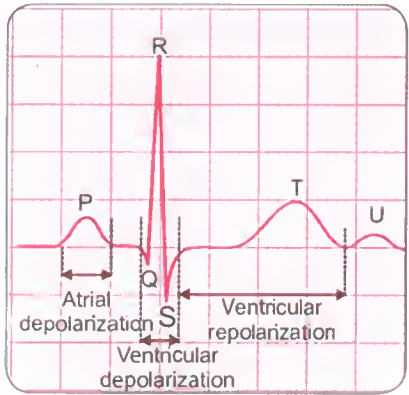


Fig. 21.4: Depolarization and repolarization depicted as deflections (Note: Atrial repolarization is buried in the QRS complex)

- Remember that each small square on the ECG paper = **0.04 seconds**.
- So if there is any question like—“Distance between P wave and QRS complex is 7 small squares”—it would be = 0.28 seconds = prolonged PR interval.
- You can use this info for any similar question.

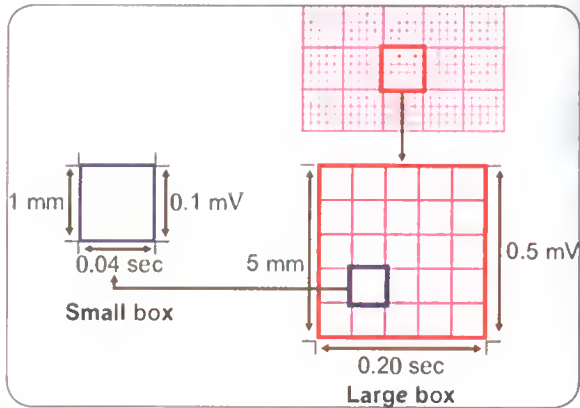


Fig. 21.5: The enlarged illustration of the electrocardiography paper. 1 small square = 1 mm; 5 small squares = 1 big square; Vertically, 1 small square = 0.1 mV. 5 of them = 0.5 mV; Horizontally, 1 small square = 0.04 sec. 5 of them = 0.2 sec

EXTRA EDGE

- Many factor influence ventricular repolarization, so the **T wave** is the **most labile** (i.e. unstable) wave of the ECG and problematic to analyze.
- Lewis leads is a special bipolar chest lead with the right arm electrode applied to the right side of the sternum at the second intercostal space and the left arm electrode applied to the fourth intercostal space adjacent to the sternum—useful in diagnosis of atrial flutter or wide QRS tachycardias.
- His Bundle Electrogram is recorded by positioning an electrode across the tricuspid valve:
 - A wave: right atrial activation (AV node activation)
 - H wave: activation of His bundle
 - V wave: ventricular electrogram

Calculation of Heart Rate on ECG

- The ECG paper moves by 25 small squares in 1 second (**speed = 25 mm/sec**). In other words, it moves by 25 X 60 = **1500** small squares in 60 seconds (1 minute). If the distance between two successive QRS complexes (**RR**

interval) is measured, the number of ECG complexes in 1 minute will be 1500 divided by that number. This gives us the heart rate in **beats per minute** (bpm).

- **Example:** The RR interval is 20 mm, hence the heart rate is 1500/20 = 75 bpm; The RR interval is 30 mm, hence the heart rate is 1500/30 = 50 bpm.



Fig. 21.6: Calculation of the heart rate from RR interval if RR interval = 25 mm; Heart rate = 60/min

ECG – Abnormalities

HyperKalemia	Tall, tented T-wave, decreased P-wave amplitude, widening of QRS, “sine wave pattern” (severe hyperkalemia causing cardiac arrest) (“Cadbury’s PERK with Tea”)
Hypokalemia	Prominent U-waves , small T-waves, ventricular bigeminy, Pseudo P Pulmonale
Hypercalcemia	Shortens Q-T interval
Hypocalcemia	Lengthens Q-T interval
Subarachnoid hemorrhage	Marked QT prolongation with deep, wide T-wave inversions (“ CVA T-wave ”)
Hypothermia	Convex elevation of J point (J waves or Osborn waves)
Pericardial effusion	Total electrical alternans (often with tamponade)
TCA overdose	Sinus tachycardia with QRS and QT prolongation.
Digoxin effect	Shortened QT interval with a characteristic “scooping” of the ST-T wave complex ST depression PR prolongation Inverted T-wave (inverted check mark sign) in V5-6 (“QT (cutie!) Chhoti, depressed ST, Prolonged PR , ultra T)
Pulmonary embolism	MC: Sinus tachycardia with an otherwise normal ECG There may be deep S-waves in I, pathological Q-waves in III, inverted T-waves in III (“SIQIIITIII”), strain pattern V1-V3, right axis deviation, RBBB, atrial fibrillation.
Syn. a/w prolonged QT interval	Romano ward syn. (AD) and Jervell Lange Nielsen syn. (AR, congenital deafness)
Lev’s disease and Lenegre’s disease	Degenerative diseases commonly responsible for damage to the specialized conducting system and produce AV block usually associated with bundle branch block
Right bundle branch block (RBBB)	More common than LBBB; RBBB occurs with heart disease, both congenital (e.g. atrial septal defect) and acquired (e.g. valvular, ischemic).

Contd

Left bundle branch block (LBBB)	LBBB is often a marker of one of four underlying conditions: ischemic heart disease, long-standing hypertension, severe aortic valve disease, and cardiomyopathy.
Tricuspid atresia	RA enlargement, left-axis deviation and LV hypertrophy.
P pulmonale	Tall peaked P waves (> 2.5 mm) a/w right atrial enlargement and COPD (increased amplitude of P wave)
P mitrale	Broad, notched P wave with a duration > 0.12s Indicating left atrial enlargement that is commonly a/w mitral stenosis (increased duration of P wave)

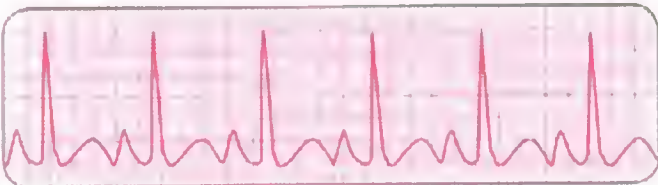


Fig. 21.7: P pulmonale: Tall and peaked P wave

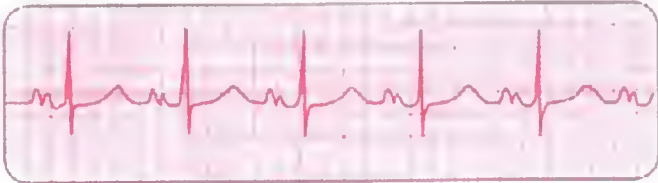


Fig. 21.8: P mitrale: Broad and notched P wave

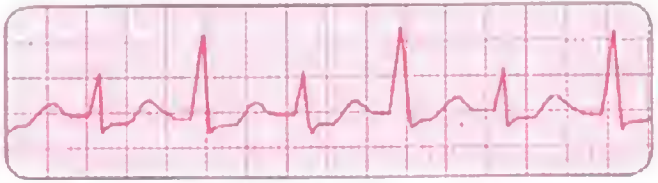


Fig. 21.9: Electrical alternans: Varying voltage of the QRS complex



Fig. 21.10: Effect of hyperkalemia on the T wave

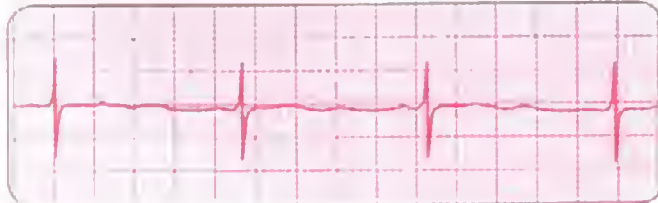


Fig. 21.11: Prominent U wave due to hypokalemia

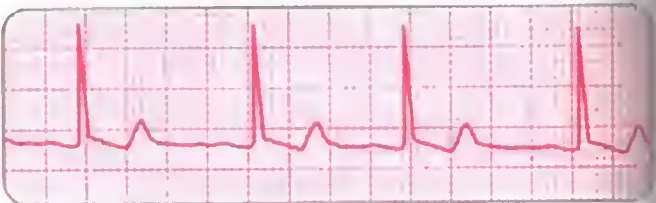


Fig. 21.12: Effect of digitalis on the ST segment

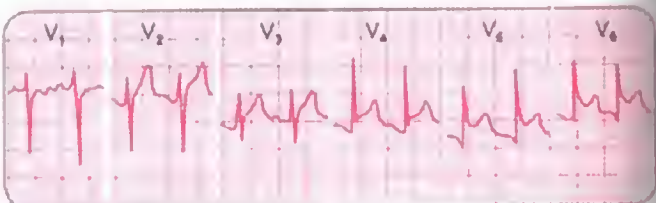


Fig. 21.13: Acute pericarditis: Saddle-shaped ST segment elevation

Axis Deviations

- Normally, the QRS axis ranges from -30° to $+100^{\circ}$.
- **Left axis deviation** = An axis more negative than -30° .
- **Right axis deviation** = An axis more positive than $+100^{\circ}$

Left axis deviation	Right axis deviation
<ul style="list-style-type: none">• Normal variant• Left ventricular hypertrophy (more common)• Block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock)• Inferior myocardial infarction• Expiration• Lying down• Obesity	<ul style="list-style-type: none">• Normal variant (particularly in children and young adults)• Spurious finding due to reversal of the left and right arm electrodes• Right ventricular overload (acute or chronic)• Infarction of the lateral wall of the left ventricle• Dextrocardia,• Left pneumothorax, or• Left posterior fascicular block• Inspiration• Tall lanky people• Standing up

RHEUMATIC HEART DISEASE

- **Late sequel of rheumatic fever is rheumatic heart disease** which affects heart valves - **mitral valve (MC)** > aortic >> tricuspid (high-pressure valves affected most);
- **Mitral regurgitation** is the **MC** disease.; rheumatic aortic stenosis is very rare in childhood.
- **Aschoff bodies**: focal inflammatory nodules most characteristic in the heart but may occur elsewhere; pathognomonic of rheumatic fever

- **MacCallum's plaques**—are subendocardial collections of Aschoff nodules, usually in the left atrium.
- **Anitschkow's myocytes**: large activated histiocytes.
- **Soldier's plaque**: thick, pearly, nonadherent epicardial plaque which is a fibrosis resulting from healed/chronic pericarditis.
- Rheumatic fever and revised 2015 Jones criteria have been covered in pediatrics chapter (Pg 678).

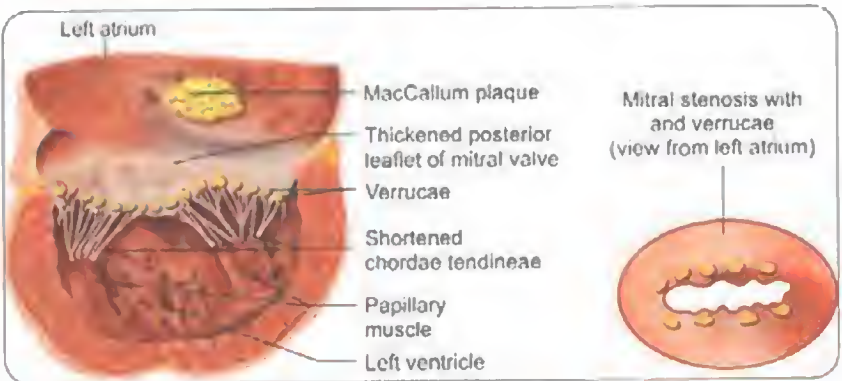


Fig. 21.14: Gross appearance of mitral valve and left atrium in RHD

Summary of Common Valvular Heart Lesions

Lesion	Clinical features	Treatment/Remarks
Mitral stenosis (MS) MC due to RHD	<ul style="list-style-type: none">• Initially asymptomatic for 1st 10 years of condition; later heart failure symptoms (dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea); hemoptysis.• Opening snap after S2; rumbling late diastolic murmur (best heard at apex), loud S1, possible peripheral edema and hepatomegaly• CXR shows RVH, Left Atrial enlargement (LAE), double aortic shadow, mitral valve calcifications. (see radiodiagnosis chapter for more)• ECHO shows ↓ mobility of mitral valve• Ortner synd.(cardiovocal synd): hoarseness of voice due to recurrent laryngeal nerve compression by LAE• Lutembacher synd: MS+ASD (secundum type) with left to right shunt	<ul style="list-style-type: none">• Diuretics (to reduce preload). Antiarrhythmics and anticoagulants if Afib develops• If advanced, balloon valvuloplasty, valve replacement.
Mitral regurgitation (MR) Due to mitral valve prolapse, RHD, papillary muscle dysfunction, endocarditis, left ventricle dilation	<ul style="list-style-type: none">• Long asymptomatic period, MC a chronic condition; when severe or acute presents heart failure symptoms (as above)• Harsh, high pitched, blowing, holosystolic murmur radiating from apex to axilla; soft S1; S3; midsystolic click• CXR shows LVH, LAE• ECHO determines cause of MR and EF	<ul style="list-style-type: none">• Anticoagulants, vasodilators• If acute MR, surgery is required.• For chronic MR, replace valve when symptomatic or EF is falling

Contd

Contd...

Lesion	Clinical features	Treatment/Remarks
Aortic stenosis (AS) Due to congenital heart disease , RHD,	<ul style="list-style-type: none"> Heart failure symptoms Exertional angina, dizziness and syncope Crescendo-decrescendo ejection systolic murmur radiating to carotids (murmur ↓ during Valsalva); ejection click; weak S2; pulsus parvus et tardus (small and slow carotid upstroke), CXR may show calcified valves ECHO shows valve condition and obstruction to flow of blood 	<ul style="list-style-type: none"> Avoid over-diuresis, Avoid vasodilators such as nitrates and ACEIs β-blockers help to reduce cardiac workload against the obstruction Valve replacement surgery for all symptomatic patient
Aortic regurgitation (AR) Tertiary syphilis , aortic root dilation, aortic dissection, RHD, congenital heart disease, endocarditis, ankylosing spondylitis, Marfan's	<ul style="list-style-type: none"> Usually asymptomatic until advanced, then presents with heart failure symptoms Bounding pulses, widened pulse pressure; late diastolic rumble (Austin-Flint murmur), capillary pulsations in nail beds that become more visible with application of pressure (Quincke's sign); pulsatile head bobbing (de Musset's sign), visible arterial pulsation in neck (Corrigan's sign), 'pistol shot' sound on auscultating over femoral artery (Traube's sign), uvular pulsation (Muller's sign) CXR shows aortic dilation and LVH ECHO shows valve abnormalities and backflow of blood 	<ul style="list-style-type: none"> Afterload reduction with ACEIs, hydralazine Valve replacement if symptomatic or if ↓ EF
Mitral valve prolapse (MVP)	<ul style="list-style-type: none"> Asymptomatic Midsystolic click, murmur if MR also present A/w with palpitations, panic attacks 	<ul style="list-style-type: none"> Endocarditis prophylaxis NOT required

Key: ACEIs = Angiotensin Converting Enzyme Inhibitors; Afib = Atrial Fibrillation; CXR = Chest X Ray; ECHO = Echocardiogram; LAE = Left Atrial Enlargement, LVH = Left Ventricular Hypertrophy, RHD = Rheumatic Heart Disease.

EXTRA EDGE

- For all above conditions (except MVP), prophylactic antibiotics should be given before any intervention with risk of bleeding, to reduce risk of accidental valve infection.
- MC cause of valvular heart disease is rheumatic heart disease—can cause MS, MR, AS, AR and TR, TS; but PS is almost always congenital (and NOT rheumatic).

CARDIAC ARRHYTHMIAS

Sinus Bradycardia

- In adults, the **normal sinus rate** under basal conditions is **60 to 100 beats per minute**.
- It occurs during episodes of hypervagotonia (**vasovagal syncope**); severe **hypoxia**; **hypercapnia**, **acidemia**, and acute **hypertension**.

Sinus bradycardia is a/w

- Hypothyroidism
- Hypothermia
- Advanced liver disease
- Typhoid fever
- Brucellosis

Atrial Fibrillation

- Risk factors: CAD, HTN, Anemia, Pulmonary disease (embolism, COPD), hyperThyroidism, Ethanol, Rheumatic heart disease, Sepsis. ("CHAPTERS").
- Clinically:**
 - Loss of a waves in the JVP
 - Absent P waves on the ECG,
 - Irregularly irregular pulse.
- Treatment: "ABCD"
 - Anticoagulate
 - β-blockers, CCBs or Digoxin for slowing of ventricular rate
 - Cardioversion: **electrical cardioversion is the treatment of choice** if the patient's clinical status is severely compromised.

Paroxysmal Supraventricular Tachycardia (PSVT)

- Tachycardia** (> 100 beats/min) arising in the atria or AV junction; occurs **MC in young adults** with **otherwise healthy hearts**; cause frequently is **AV nodal reentry anomaly**.
- Clinically: sudden palpitations, dyspnea or syncope, ECG shows P waves hidden in T waves; in WPW syn. Delta waves are seen.

- Treatment: **IV adenosine is drug of choice**; or CCBs (verapamil).

Heart Block

Anomaly	Comments
I degree heart block	<ul style="list-style-type: none"> AV nodal block Constantly lengthened PR interval >0.2s. Seen in digoxin toxicity NO treatment needed.
Mobitz type 1 (Wenckebach)	<ul style="list-style-type: none"> AV nodal block Progressively lengthening PR interval followed by a dropped/lost QRS Relatively common NO treatment needed.
Mobitz type 2	<ul style="list-style-type: none"> Defect in His-Purkinje system Constant PR interval with dropped QRS beats Ventricular pacemaker required even if asymptomatic! Digoxin does NOT cause Mobitz type 2 block
III degree heart block (Complete heart block)	<ul style="list-style-type: none"> Present when no atrial impulse propagates to the ventricles, i.e. no relation between P and QRS waves; ventricles contract independently! Seen in Inf. wall MI, digitalis toxicity, Lenegre's disease, ankylosing spondylitis Ventricular pacemaker required even if asymptomatic!



Fig. 21.15: First degree A-V block—ECG



Fig. 21.16: Second degree A-V block Mobitz type 1—ECG

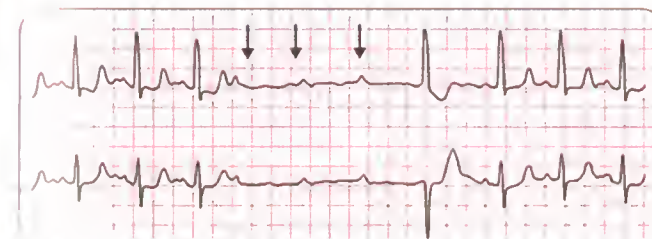


Fig. 21.17: Second degree A-V block Mobitz type 2—ECG



Fig. 21.18: Third degree A-V block—ECG

QT Interval

- The QT interval measures the **duration of electrical activation** and **recovery of the ventricular myocardium**.
- The QT interval varies inversely with cardiac rate. Therefore the 'normality' of the QT interval can be determined only by correcting for the cardiac rate.
- The **corrected QT interval (QTc interval)** is included in routine ECG analysis and is calculated by **Bazett's formula**.

$$QTc = QT / \sqrt{RR \text{ interval (in seconds)}}$$

- The upper limit of the QTc interval is approximately **0.46 s (460 ms) in women** and **0.45 s (450 ms) in men**.
- The QTc interval is slightly **longer in females**, **longer during sleep** and **increases slightly with age**.

Torsades de Pointes

- The ECG hallmark of **polymorphic ventricular tachycardia (torsades de pointes, 'twisting of points')** is a **QTc prolongation** often in **excess of 0.6 seconds (600 ms)**.
- Causes of prolonged QTc interval: **Hypokalemia**, **Hypomagnesemia**, **Hypocalcemia**, **Renal failure**, **Heart failure**, **Drugs** (see table below).
- Treatment: **IV Magnesium**.

Drugs Causing Prolonged QTc (Torsades de Pointes)

Class of drug	Known examples
Anti-arrhythmic Class 1A	Disopyramide, Procainamide, Quinidine
Anti-arrhythmic Class 3	Amiodarone, Bretylium, Sotalol, Dofetilide, Ibutilide
Antimicrobial	Erythromycin, Clarithromycin, Trimethoprim-Sulfamethoxazole
Antifungal	Fluconazole, Ketoconazole, Itraconazole
Antimalarial or antiprotozoal	Chloroquine, Halofantrine, Mefloquine, Pentamidine, Quinine
Antihistamine	Terfenadine, Astemizole, Diphenhydramine
GI prokinetic	Cisapride

Contd

Contd...

Class of drug	Known examples
Psychoactive	Chloral hydrate, Haloperidol, Lithium, Phenothiazines, Pimozide, Tricyclic anti-depressants
Anti-HIV	Efavirenz
Miscellaneous	Amantadine, Indapamide, Probulcol, Tacrolimus, Vasopressin

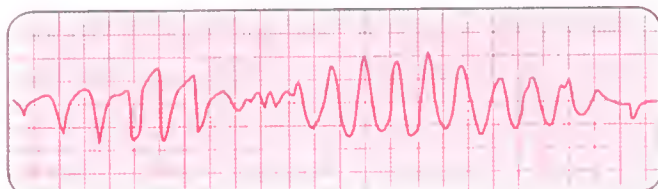


Fig. 21.19: Polymorphic ventricular tachycardia ('Torsade de pointes')

Congenital Long QT Syndrome

- Due to defect in potassium or sodium channels
- Can lead to *torsades de pointes* and sudden death. Two types are:
- **Romano Ward syndrome** (MC):
 - AD, a/w syncope, sudden death, sometimes seizures; diabetes, asthma, syndactyly.
- **Jervell and Lange Nielsen syndrome**:
 - AR, all features as above + severe sensorineural deafness.

EXTRA EDGE

- **Brugada syndrome**: a rare syndrome characterized by > 0.2 mV of ST-segment elevation with a coved ST segment and negative T wave in more than one anterior precordial lead (V1-V3) and episodes of syncope or cardiac arrest due to polymorphic VT in the **absence of structural heart disease**. Cardiac arrest may occur during sleep or be provoked by febrile illness. Males are MC affected. Mutations involving cardiac sodium channels are identified in approximately 25% of cases.

Wolff-Parkinson-White (WPW) Syndrome

- **Pathophysiology**: There is an **abnormal band of atrial tissue which connects the atria and ventricles** and can electrically bypass the AV node (**Bundle of Kent**).
- **Avoid digoxin and verapamil** since it shortens refractory period and causes increased conduction in the bypass tract.
- **ECG**: **Shortening of the PR interval, wide QRS complex** with a slurring of the QRS complex called a '**delta**' wave.
- Treatment of choice: **Transcutaneous radiofrequency catheter ablation**.

EXTRA EDGE

- **Lown Ganong Levine syndrome**: Another pre-excitation syndrome with **short PR interval**, normal QRS complex with NO delta waves.

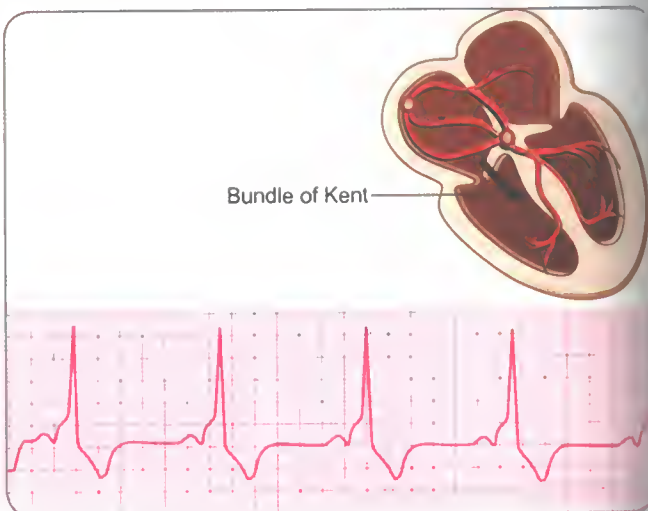


Fig. 21.20: Short PR interval: WPW syndrome

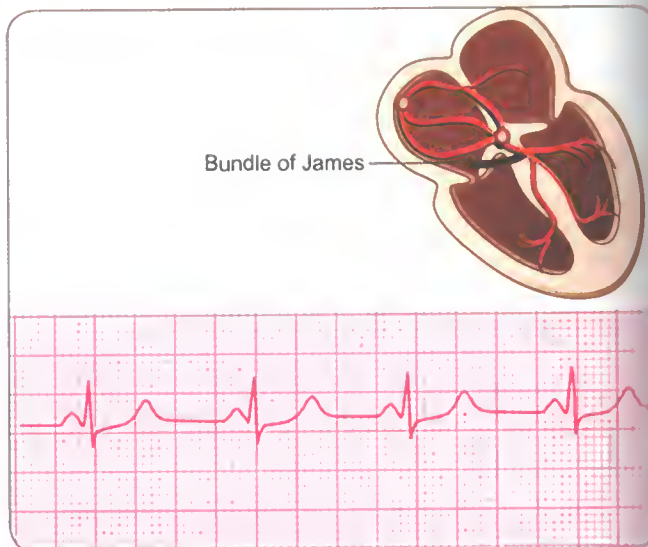


Fig. 21.21: Short PR interval: LGL syndrome

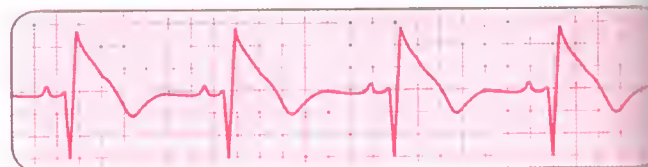


Fig. 21.22: Brugada syndrome: rSR' pattern in lead V₁; normal rSII' duration; Elevated ST segment; inverted T wave

Contd...

Treatment of Cardiac Arrhythmias

- **Anti-arrhythmic drugs** have been discussed under **Pharmacology chapter (Pg 333)**.

Features of Cardiac Syndrome X

- **Angina** typically on effort and severe enough to suggest IHD
- '**Ischemia-like**' **ST-segment depression** during angina or provocation tests
- **Normal coronary arteries** at angiography
- Absence of epicardial arterial spasm and of known causes of microvascular dysfunction
- **Excellent prognosis** and no increase in risk of major cardiac events.

CONGESTIVE HEART FAILURE

- Definition: Heart failure (HF) as a complex clinical syndrome resulting from structural or functional **impairment of ventricular filling or ejection of blood**, which in turn leads to the **cardinal clinical symptoms** of **dyspnea** and **fatigue** and **signs of HF**, i.e. **edema** and **rales**.
- Because many patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over the **older term** "congestive heart failure."
- In developed countries, coronary artery disease (CAD) is MC cause of HF.
- **Rheumatic heart disease** remains a major cause of HF in **Africa** and **Asia**.
- **Cor pulmonale**: Right ventricular failure due to chronic lung disease and is triggered by the onset of pulmonary hypertension (a.k.a pulmonary heart disease).
- The MC cause of right HF is **left HF**!

Etiology of HF

Depressed Ejection Fraction (<40%)	Preserved Ejection Fraction (>40–50%)
<ul style="list-style-type: none">• Coronary artery disease (Myocardial infarction, Myocardial ischemia)• Chronic pressure overload (Hypertension, Obstructive valvular disease)• Chronic volume overload (Regurgitant valvular disease; Intracardiac (left-to-right) shunting; Extracardiac shunting)• Chronic lung disease (Cor pulmonale, Pulmonary vascular disorders)	<ul style="list-style-type: none">• Pathologic hypertrophy (HOCM, hypertension)• Aging• Restrictive cardiomyopathy• Infiltrative disorders (amyloidosis, sarcoidosis)• Storage diseases (hemochromatosis)• Fibrosis• Endomyocardial disorders

Contd...

Depressed Ejection Fraction (<40%)	Preserved Ejection Fraction (>40–50%)
------------------------------------	---------------------------------------

- Nonischemic dilated cardiomyopathy (Familial/genetic disorders, Infiltrative disorders)
- Toxic/drug-induced damage (Metabolic disorder, Viral)
- Chagas disease
- Arrhythmias (Chronic bradyarrhythmias, Chronic tachyarrhythmias)

High-Output States

- Thyrotoxicosis
- Nutritional disorders (beriberi)
- Systemic arteriovenous shunting
- Chronic anemia

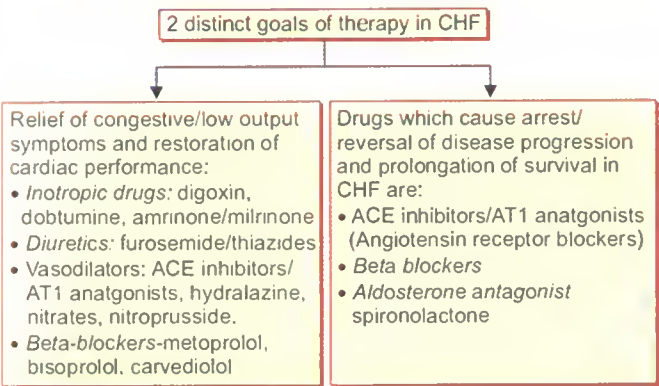
Clinical Features

- Fatigue
- Dyspnea (shortness of breath);
- Exertional dyspnea first and later **Orthopnea** (dyspnea in recumbent position)
- **Paroxysmal Nocturnal Dyspnea (PND)**: Acute episodes of severe dyspnea and coughing that generally occur at night and awaken the patient from sleep, usually 1–3 h after the patient retires. Whereas orthopnea may be relieved by sitting upright at the side of the bed with the legs in a dependent position, patients with PND often have persistent coughing and wheezing even after they have assumed the upright position.
- Cheyne-Stokes respiration
- Acute pulmonary edema
- Raised JVP
- Pulmonary crepitations (crackles or rales)
- Cardiomegaly
- Hepatomegaly
- Peripheral edema.

Investigations

- Chest X-ray: See Radiodiagnosis chapter.
- 2-D ECHOCardiography: most useful index of LV function is the EF (stroke volume divided by end-diastolic volume).
- Biomarkers of CHF: B-type natriuretic peptide (BNP); N-terminal proBNP (NT-BNP); C reactive protein (CRP); TNF; Troponin T and I, galectin-3, soluble ST2.

Treatment of Congestive Heart Failure



Newer Drugs for Heart Failure

Ivabradine

- Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I(f) 'funny' current, which regulates heart rate.
- Indicated in stable patients with symptomatic chronic heart failure with resting heart rate ≥ 70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to β-blocker use.

Combination Sacubitril + Valsartan

- **Sacubitril** is an **angiotensin-neprilysin inhibitor** used along with ARB valsartan.

PRIMARY PULMONARY HYPERTENSION

- Defined as **mean pulmonary artery pressure of 25 mm Hg or more** with a pulmonary capillary wedge pressure (PCWP) of < 16 mm Hg at rest.
- Characterized by **pulmonary vascular obstructive disease and right-sided heart failure**.
- RVH → Dilated pulmonary artery → Pulmonary insufficiency → tricuspid insufficiency (late stages).
- Predominant symptoms include **exercise intolerance and easy fatigability**. **Ejection click after S1** is present and **S2 is closely split**.
- Chest X-ray – **prominent pulmonary artery and right ventricle**. ECG – **spiked P waves**.
- Treatment:

- **Calcium channel blockers** (nifedipine);
- **Prostacyclins (PGI2):** IV (**epoprostenol**) or IV/SC (**treprostinil**) or **nebulized/inhaled (iloprost)**
- **Oral endothelin antagonist** (**Bosentan, Macitentan**) and **Ambrisentan** (selective ET-A receptor),
- **Oral PDE-5 inhibitor** (**sildenafil, tadalafil**).
- **Oral Riociguat** (**guanylate cyclase stimulator**).
- **Definitive therapy** for non-responders **lung transplantation**.

ANGINA

- **Stable Angina**
 - It is characterized by chest or arm discomfort that may not be described as pain but is reproducibly **a/w physical exertion or stress** and is **relieved within 5–10 min by rest** and/or **sublingual nitroglycerin**.
 - Benefited by beta blocker treatment.
 - **Ranolazine** is an antianginal drug that decreases myocardial ischemia by inhibiting **late inward sodium current**.
- **Unstable Angina**
 - It is defined as angina pectoris or equivalent ischemic discomfort with at least one of three features:
 - It **occurs at rest** (or with minimal exertion), usually **lasting >10 min**;
 - It is severe and of **new onset** (i.e., within the prior 4–6 weeks); and/or
 - It occurs with a **crescendo pattern** (i.e., distinctly more severe, prolonged, or frequent than previously).
 - Unstable angina **requires treatment** to avoid evolution into an MI.

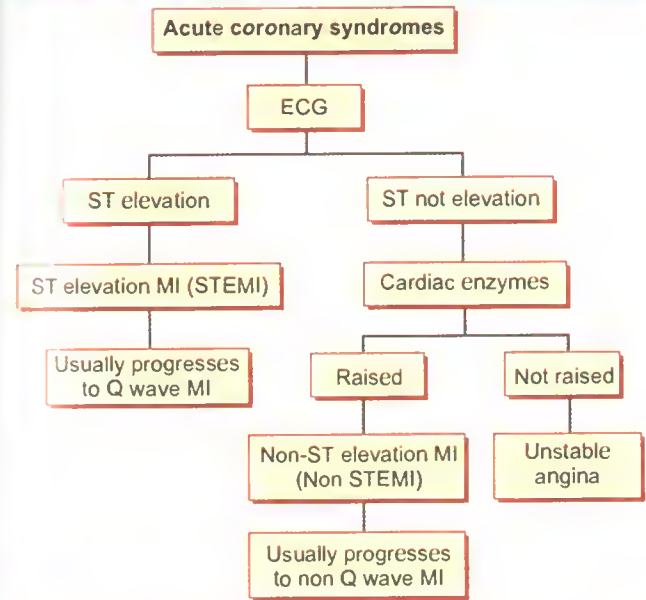
Prinzmetal Angina (Variant, vasospastic angina)

- A syndrome of ischemic pain that **occurs at rest but NOT usually with exertion!** and is a/w transient **ST-segment elevation**.
- This syndrome is due to **focal spasm of an epicardial coronary artery**, leading to severe myocardial ischemia.
- Pain wakes up patient at night.
- **Nitrates and calcium channel blockers** are the main treatments.
- **Beta blockers** are **contraindicated** since they may worsen vasospasm.

Treatment of Angina

- **Anti-anginal drugs** have been discussed under **Pharmacology chapter (Pg 329)**.

MYOCARDIAL INFARCTION (MI)



NON-ST ELEVATION MI (NON-STEMI)

- Acute coronary syndromes without ST segment elevation (non-STEMI) do not have an acute coronary occlusion and hence **fibrinolytic therapy should be avoided** in such patients since it may be harmful (unlike in STEMI where fibrinolytic therapy IS indicated).
- **Antiplatelet and anticoagulation** therapies and **percutaneous coronary intervention** are the mainstay of treatment.

ACUTE MYOCARDIAL INFARCTION WITH ST ELEVATION (STEMI)

- **STEMI** results **MC from occlusive coronary thrombus** (at the site of pre-existing atherosclerotic plaque).
- Other rarer causes include **prolonged vasospasm; inadequate myocardial blood flow (hypotension); embolic occlusion; aortic root dissection and vasculitis**. (STEMI in young people without risk factors—think of **cocaine**).
- **ST elevation** denotes **an acute coronary occlusion** and **needs immediate reperfusion** therapy.

Clinically

- **Premonitory pain:** Worsening of angina and angina occurs with minimal exertion/rest.
- Unlike angina, most acute MIs occur at rest in **early morning**.
- Pain of infarction: Acute chest pain worsening within few minutes (**tightness** or 'elephant on chest'); patients places fist over the chest (**Levine sign**); pain is **not** responsive to nitroglycerine.
- Sweating, nausea, vomiting, cough may be present.
- Atypical/**silent MI** may be seen in **diabetics, older patients and women**.
- Tachycardia, hypotension, rales, **new S4** heart sound, **new systolic murmur**.
- **Chest pain** (tightness or 'elephant on chest')-patients places fist over the chest (**Levine sign**).
- Sweating, nausea, vomiting; **in diabetics**, presentation maybe **atypical/silent MI**.
- Tachycardia, hypotension, rales, **new S4 heart sound, new systolic murmur**.

ECG OF MI

- Within hours, T-wave may become abnormally tall and the ST segment may begin to rise.
- Within 24 hours the **T-wave inverts** as the **ST elevation** begins to resolve
- Pathological **Q-waves** also begin to form within a few days. (hence pathological **waves indicates old infarction**)
- T-wave inversion may or may not persist.
- ST elevation rarely persists except with a ventricular aneurysm.
- In **subendocardial infarction** (inner half of myocardium involved) ST segment depression is seen and NO pathological waves are seen.
- ECG is **most sensitive** to detect **acute occlusion of the LAD** (left anterior descending) and is **least sensitive** for involvement of the **circumflex coronary** artery.
- **MC vessel** thrombosed in **acute MI** is **LAD** (~50% cases)- leads to ST segment elevation.
- ST elevation in a subepicardial lesion is called '**Pardee's sign**'

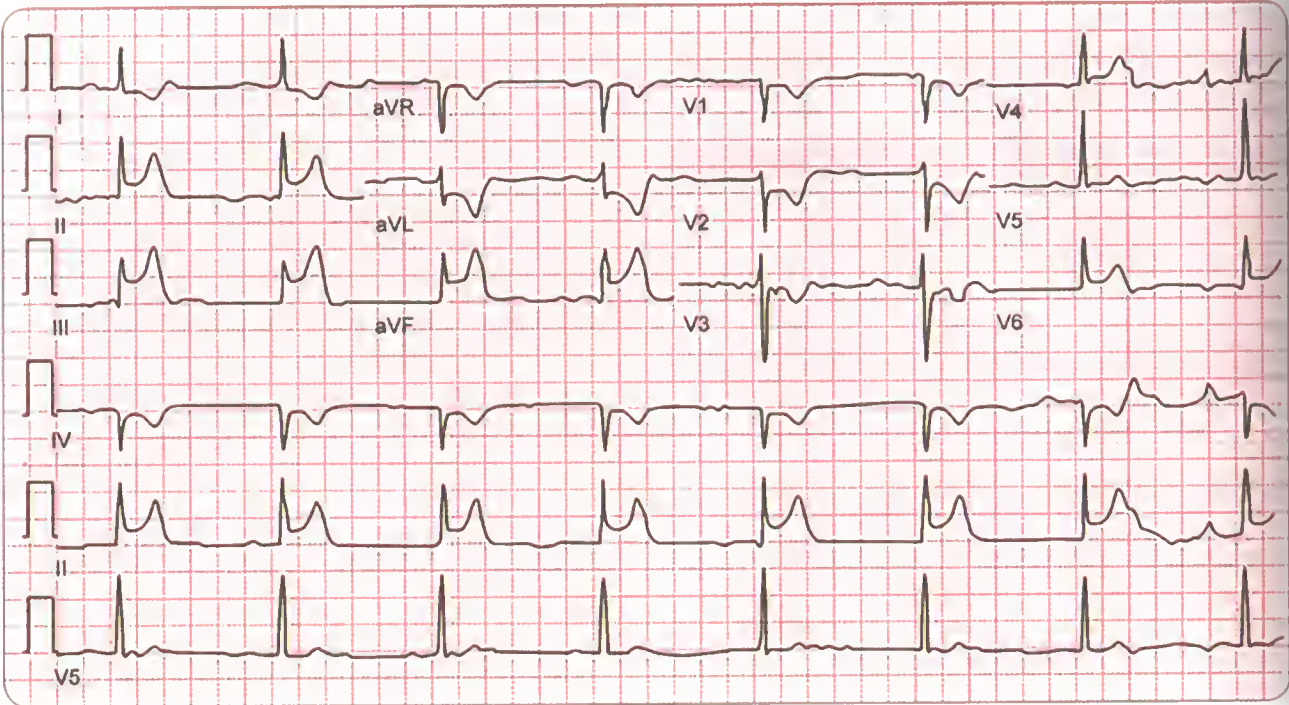


Fig. 21.23: Inferior wall myocardial infarction (IWMI). ST segment elevation in leads II, III and aVF, T wave inversion in leads III and aVL, pathologic Q waves in lead L III and reciprocal ST depression in L I, aVL, V3, V4, V5

Troponin

- **Troponin** is a contractile protein, normally is not found in serum, is released only when myocardial necrosis occurs.
- **Cardiac specific troponin T (cTnT) and troponin I (cTnI)** – (especially, **cTnI**) has **greatest sensitivity and specificity in detecting MI**, better than CKMB, hence used as serum markers of acute MI.
- Also the optimum biomarker for the evaluation of patients with MI who have coexistent skeletal muscle injury.
- Best biomarker for Myocardial **re-infarction** = **Troponin I**.

Creatine Phosphokinase

- **Fisrt enzyme released** into circulation after acute MI.
- Creatine kinase comprises 3 isoenzymes, including:
 - **CK-MM**, which is found mainly in **skeletal muscle**;
 - **CK-BB** predominantly found in the **brain**
 - **CK-MB**, which is found mainly in the **heart**.

Marker	Onset	Peak	Normalization	Significance
Troponins T and I	2–4 hours	48 hours	7–10 days	MOST specific and sensitive

Contd...

Contd...

Marker	Onset	Peak	Normalization	Significance
CK-MB	2–4 hours	24 hours	72 hours	Sensitive but NOT specific BEST biomarker for reinfarction
LDH	24–48 hours	Many days	7–14 days	Nonspecific marker
Myoglobin	2 hours	4 hours	8–12 hours	Earliest marker Nonspecific to cardiac muscle

EXTRA EDGE

- Serum normally contains slightly more LDH2 than LDH1. An LDH1 > LDH2 is called a **“flipped LDH”** pattern – seen in **acute MI**.

Treatment of MI

- **Aspirin:** All patients with suspected or acute MI must receive aspirin (162 or 325 mg) at once irrespective of whether fibrinolytic therapy is considered or whether the patient was taking aspirin earlier.

- **Antiplatelets (P2Y12 inhibitors):** Prasugrel, Ticagrelor and Clopidogrel. Recent guidelines call for a P2Y12 inhibitor to be added to aspirin irrespective of whether fibrinolytic therapy is considered and continued for at least 14 days (generally 1 year).
- **Reperfusion therapy:** Patients with STEMI who seek medical attention within 12 hours of onset of symptoms must be treated with reperfusion therapy—either primary Percutaneous Coronary Intervention (PCI) or fibrinolytics.
- **Analgesia:** **Morphine**
- **Oxygen:** Low flow oxygen.
- **Beta-blockers:** **Metoprolol or carvedilol**.
- **Nitrates:** **Nitroglycerine** for recurrent ischemic pain and also lowers BP.
- **ACE inhibitors** and ARBs (valsartan)
- **Calcium channel blockers:** Unlike beta-blockers, **calcium antagonists are of very little value** in the acute setting, and there is evidence that short-acting dihydropyridines (nifedipine) may be a/w an increased mortality risk.
- **Statins** [Early administration of high dose statin therapy (pravastatin or atorvastatin) has been shown to reduce the risk of recurrent ischemic events during the 4-month period following hospital discharge].
- **Antithrombotic therapy:** Long-term aspirin + antiplatelets.

EXTRA EDGE

- Mnemonic for treatment: **“BeMOAN”** = **B**eta-blockers, **M**orphine, **O**xygen, **A**spirin + **A**CE inhibitor, **N**itroglycerine.

Currently approved fibrinolytic agents

- **Streptokinase, Urokinase, Anistreplase** (acylated plasminogen streptokinase activator complex)
- **Alteplase or activase** (recombinant tissue-type plasminogen activator (rt-PA))
- Recombinant derivatives of rt-PA, **tenecteplase** (TNK-tPA) and **reteplase**.

More about Fibrinolytic Agents

- **Clot selective/Clot specific (fibrin-specific plasminogen activators):** **Alteplase, tenecteplase** (TNK-tPA) and **reteplase**.
- **Nonspecific agents:** **streptokinase, anistreplase, and urokinase**.
- Alteplase is **faster and shorter acting**, t1/2 is 4–8 minutes compared to streptokinase which has t1/2 of 30–80 minutes.

- **Allergic reactions hypotension and fibrogenolysis** are more with **streptokinase**.
- **Tranexamic acid** is an **antifibrinolytic**. It works by preventing blood clots from breaking down too quickly. This helps to reduce excessive bleeding.

Pathology of Acute MI

- For the **first ~30 minutes no change at all** can be seen by gross examination or by light microscopy in histopathology.
- **On electron microscopy**
 - **Reversible phase (first 30 minutes):** relaxed myofibrils, glycogen depletion and mitochondrial swelling.
 - **Irreversible phase (after first 30 minutes):** sarcolemmal disruption, mitochondrial amorphous densities.

Time from onset	Gross examination	Microscopically	Comments
2–3 hours		Wavy myocardial fibres Staining defect with tetrazolium or basic fuchsin dye	
4–12 hours		Coagulation necrosis with loss of cross striations, contraction bands, edema, hemorrhage, early neutrophilic infiltrate	
18–24 hours	Pallor of myocardium	Continuing coagulation necrosis, pyknosis of nuclei, marginal contraction bands	Risk for arrhythmia
24–72 hours	Pallor with some hyperemia	Total loss of nuclei and striations dense neutrophilic infiltrate	
3–7 days	Hyperemic border with central yellowing	Macrophage and mononuclear infiltration begin, fibrovascular response begins	Risk for ventricular wall rupture

Contd

Contd...

Time from onset	Gross examination	Microscopically	Comments
10–21 days	Maximally yellow and soft with vascular margins	Fibrovascular response Prominent granulation tissue	
6 weeks	White fibrosis	Fibrosis	Risk for ventricular aneurysm

EXTRA EDGE

- **Triphenyltetrazolium Chloride (TTC)** is a gross histochemical dye that can identify infarcted myocardium **within 2–3 hours of infarct**. TTC imparts **brick-red color** to intact, non-infarcted myocardium (LDH activity is high) whereas an infarct appears as an **unstained pale zone** (LDH leaks out through damaged membranes of dead cells).

Early Complications of MI

- **Arrhythmias—ventricular tachycardia or fibrillation**; greatest risk **within few hours post MI**, important cause of death before reaching hospital.
- Left ventricular failure and pulmonary edema (**Killip classification** is used to assess the severity of heart failure after AMI)
- Cardiogenic shock
- **Ventricular wall rupture** – rupture usually occurs **3–5 days post MI (due to macrophage effect)**, **more likely in anterior MI**
- **Acute mitral regurgitation—MC with an infero-posterior infarction** and may be due to ischemia, necrosis, or rupture of the papillary muscle (esp. posterior papillary muscle).
- **Right ventricular failure**—common after **infero-posterior infarcts**

Late Complications of MI

- Deep vein thrombosis

Summary of Cardiomyopathies

	Dilated/Congestive (MC)	Hypertrophic	Restrictive/Obliterative
Etiology	Idiopathic, Alcohol, Anemia (chronic), BeriBeri, Cocksackie B myocarditis, chronic Cocaine use, Chaga's disease, Doxorubicin, Peripartum, Hemochromatosis, HIV	Congenital, Autosomal dominant , a/w infant of <i>diabetic mother</i> , <i>glycogen storage disease</i> , <i>Friedrich's ataxia</i>	Amyloidosis , Sarcoidosis , Postradiation, endomyocardial fibroelastosis, <i>Löffler's synd.</i> (endomyocardial fibrosis with eosinophilic infiltrate)

- Mural thrombosis and systemic embolism
- Left ventricular aneurysm
- **Dressler's syndrome—fibrinous pericarditis** accompanied by pleural and pericardial effusions, **autoimmune** etiology, treat with NSAIDs, steroids.
- Depression.

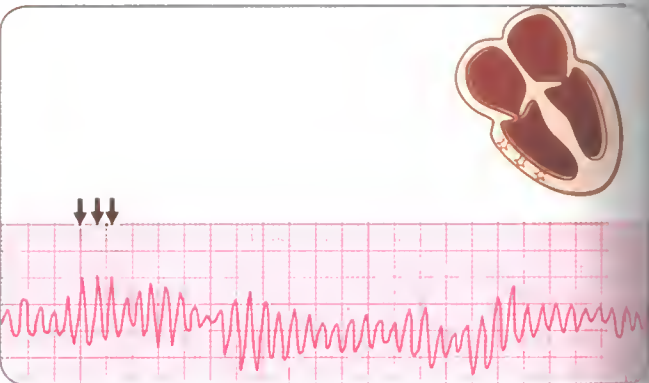


Fig. 21.24: Ventricular fibrillation: Irregular, bizarre and chaotic deflections

States of Myocardial Cells after Periods of Ischemia

Condition	Viability of cells	Cause of injury	Return of function
Infarcted	Non-viable	Prolonged ischemia	No recovery Supportive treatment
Stunned	Delayed with reperfusion	Limited ischemia	Recovery Supportive treatment
Hibernating	Viable	Ongoing ischemia	Prompt recovery Revascularization is required

EXTRA EDGE

- Best non-invasive investigation to check for viable myocardium is PET.

Contd...

Contd...

	Dilated/Congestive (MC)	Hypertrophic	Restrictive/Obliterative
Disorder	Systolic dysfunction	Diastolic dysfunction	Diastolic dysfunction
Clinical features	Left or biventricular heart failure Cardiomegaly , ↑ JVP, S3, rales	Dyspnea, chest pain , syncope, sudden death in young adults may be presenting symptoms Loud S4, holosystolic murmur, double or triple apical impulse, bisferiens carotid pulse	Dyspnea, fatigue, right heart failure , ↑ JVP, Kussmaul's sign
Investigations	CXR: dilated ' water bottle ' heart; Kerley B lines ECHO: dilated ventricular walls	ECHO: thickened septum and ventricular wall, ↑ ventricular outflow velocity	CXR: cardiomegaly and pleural effusions ECHO: ↓ in wall compliance with inspiration
Treatment	Salt and water restricted diet Diuretics, ACEIs, b-blockers, vasodilators to reduce preload and afterload	Avoid strenuous activities b-blockers, CCBs to decrease cardiac workload Left ventricular myomectomy or pacemaker implantation	Pacemaker implantation Heart transplantation is definitive cure
Mnemonic	DalSY ; D ilated = S ystolic dysfunction	HY-Fi ; H ypertrophic = F amilial	

Takotsubo Cardiomyopathy

- **Takotsubo** cardiomyopathy = **Stress induced (catecholamine) cardiomyopathy** = "**broken heart**" syndrome; affects **postmenopausal women**; presents as **acute chest pain and acute MI**; **apical left ventricular ballooning** is seen.
- Most patients recover completely.
- Treatment: include **nitrates for pulmonary edema, intraaortic balloon pump** if needed for low output, **combined alpha and beta blockers** rather than selective beta blockade if hemodynamically stable, and **magnesium for arrhythmias** related to QT prolongation.
- **Anticoagulation is generally withheld** due to the occasional occurrence of **ventricular rupture**.

Hypertrophic Obstructive Cardiomyopathy (HOCM)

- **Systolic ejection murmur of HOCM** typically is a **systolic ejection crescendo-decrescendo murmur**, which is best heard between the apex and left sternal border and radiates to the suprasternal notch but not to the carotid arteries or neck.

- **Murmur diminishes with**
 - ↑ in preload (e.g. Mueller maneuver, squatting)
 - ↑ in afterload (e.g. handgrip, passive leg raising, pregnancy).
- **Murmur increases with**
 - ↓ in preload (e.g. Valsalva maneuver, nitrate administration, diuretic administration, sudden standing) or with
 - ↓ in afterload (e.g. vasodilator administration).

Drugs to be AVOIDED in HOCM	Drugs which CAN be used in HOCM
<ul style="list-style-type: none">• Digitalis• Diuretics• Dihydropyridine calcium blockers• Nitrates• Vasodilators• β-adrenergic agonists• Alcohol ingestion	<ul style="list-style-type: none">• β-blockers ameliorate angina pectoris and syncope in one-third to one-half of patients.• Amiodarone ↓ supraventricular and ventricular arrhythmias• Nondihydropyridine calcium channel blockers (verapamil and diltiazem) and disopyramide may reduce the severity of outflow tract pressure gradients.

D/D of Constrictive Pericarditis

Feature	Cardiac Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy	Right ventricular MI
Pulsus paradoxus	Common	Rare	Rare	Rare
Kussmaul's sign	Absent	Present	Present	Present
Third heart sound (S3)	Absent	Absent	Rare	May be present
Pericardial knock	Absent	Often present	Absent	Absent
Electrical alternans	May be present	Absent	Absent	Absent
Thickened pericardium, pericardial calcification	Absent	Present	Absent	Absent
JVP				
Prominent y descent	Absent	Usually present	Rare	Rare
Prominent x descent	Present	Usually present	Rare	Rare

EXTRA EDGE

- **Beck's triad** in **cardiac tamponade** consists of distended neck veins, distant heart sound, hypotension
- In chronic constrictive pericarditis, the apical pulse is reduced and may retract in systole (**Broadbent's sign**).

INFECTIVE ENDOCARDITIS

Acute endocarditis	Subacute endocarditis
<ul style="list-style-type: none"> • S. aureus MC (high virulence) • Rapid onset • Large vegetations on previously normal valves 	<ul style="list-style-type: none"> • S. viridans (low virulence) • Insidious onset • Smaller vegetations in congenitally abnormal or diseased valves • Sequel of dental procedures

Clinical Features

- **Mitral valve MC** involved; Tricuspid valve in IV drug abusers. ("Never Tri drugs!"):
 - **Fever**
 - **Roth spots** (round white spots on retina surrounded by hemorrhage)
 - **Osler's nodes** (tender raised lesions on finger or toe pads)
 - **Janeway lesions** (small erythematous lesions on palms and soles)
 - **Splinter hemorrhages** on nail beds
 - **New murmur.**
 - **Bracht wachter bodies**-yellow white spots in myocardium
 - **Mycotic aneurysms**

Management

- Multiple **blood cultures** (3) needed for diagnosis.
- If transthoracic ECHO is negative, do **transesophageal ECHO** (more sensitive).
- **Duke criteria** (clinical, biochemical and ECHO changes) are used for Diagnosis.
- Treat with **prolonged antibiotic therapy** for 4–6 weeks.

Duke Criteria for Infective Endocarditis

Diagnostic = 2 Major Criteria OR 1 Major + 3 Minor Criteria OR 5 Minor Criteria

Major Diagnostic Criteria

- **Positive blood culture** for typical Infective Endocarditis organisms (*Strep viridans* or *havis*, *HACEK*, *staph aureus* without other primary site, *enterococcus*), from 2 separate blood cultures or 2 positive cultures from samples drawn > 12 hours apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 hour apart)
- **Echocardiogram** with oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or abscess, or new partial dehiscence of prosthetic valve or new valvular regurgitation.

Minor Diagnostic Criteria

- **Fever-Temp** > 38.0° C (100.4° F)
- **Immunologic phenomena**: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

VASCULAR DISEASES

Monckeberg's Medial Calcific Sclerosis

- Characterized by **focal calcification in the tunica media** of small to medium-sized muscular arteries **without associated inflammation**, largely sparing the **intima and adventitia**.
- The femoral, radial, ulnar and genital arteries are involved typically after age of 50 yrs; **no clinical consequences**.
- An example of **osseous metaplasia**.

Aneurysms

- **True aneurysm** = composed of all layers of the vessel wall
- **False aneurysm** (pseudoaneurysm or pulsating hematoma) = an extravascular hematoma that communicates with the intravascular space; part of the vessel wall is missing.

Atherosclerotic aneurysms

- Destruction of underlying tunica media leading to weakening of vessel wall;
- Usually occur in the **abdominal aorta** between the renal arteries and the iliac bifurcation.

Syphilitic (leptic) aneurysms

- Occur in **tertiary syphilis**, ↓ results in endarteritis obliterans → damages vasa vasorum → thoracic aortitis → aneurismal dilatation.
- Typically **confined to the thoracic aorta**. The intimal surface is wrinkled and shows a **'tree-bark' appearance**
- When the aortic valve is involved, aortic insufficiency occurs and left ventricular hypertrophy occurs due to volume overload → **massively enlarged heart** called '**cor bovinum**'.

- "AARTAD = Abdominal Aneurysms Rupture; Thoracic Aneurysms Dissect!!"
- Still, **atherosclerosis is the MC cause** of both **thoracic and aortic aneurysms** (now that tertiary syphilis is rare)
- Investigation of choice for **screening** abdominal aortic aneurysm is **Ultrasound**.
- Investigation of choice for **diagnosis** of abdominal aortic aneurysm and its rupture is **contrast enhanced CT angiography**.
- Indications for **elective aneurysm repair** based on size
 - **Ascending aorta** > 5 cm
 - **Abdominal aorta** > 5.5 cm
 - **Descending (Thoracic) aorta** > 6 cm (> 5.5 cm in patients with Marfan's syndrome)

- Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions.
- Echocardiographic findings: consistent with endocarditis but do not meet a major criterion as noted above.
- Predisposing heart condition or **intravenous drug use**
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with endocarditis (excluding coag neg staph, and other common contaminants).
- Mnemonic: "**FIVE PM**".

Vegetations on Heart Valves

Condition	Vegetation
Rheumatic heart disease	Small warty vegetations along the line of closure of valves.
Infective endocarditis	Large bulky vegetations on valve cusps that extend onto the cords.
Nonbacterial thrombotic (marantic) endocarditis	Sterile vegetations at the line of closure of valves, 2° to malignancy (mucinous adenoma Ca) or hypercoagulable state
Libman-Sacks endocarditis (LSE)	Vegetations form on both sides of valve leaflets; seen in SLE . (" SLE causes LSE! ")

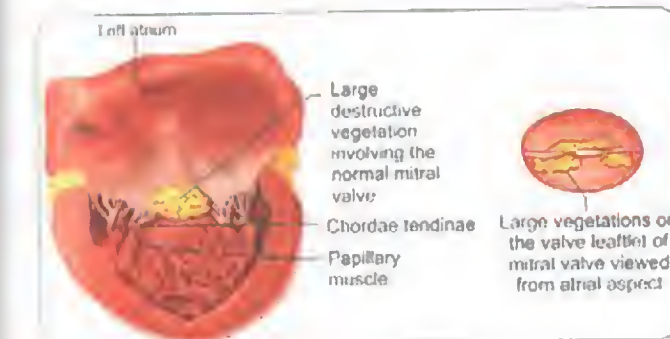


Fig. 21.25: Acute bacterial endocarditis. Mitral valve shows large friable vegetations

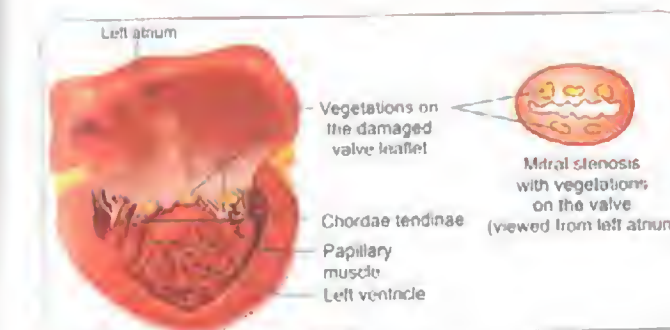


Fig. 21.26: Subacute bacterial endocarditis. Mitral valve shows vegetations

- Mnemonic: “**As(k)c Abdomen (to) Descuss** (about aneurysm repair)!” - 5, 5.5 and 6 cm.
- Rate of aneurysm expansion > **0.5 cm/year**

EXTRA EDGE

- **Cirroid aneurysm** is a type of **congenital AV malformation** found MC in **superficial temporal artery**.

Aortic Dissection

- **Intimal tears** that originate **within 10 cm from the aortic valve (90%)** or descending aorta just **distal from the subclavian artery**; blood penetrates media and accumulates between outer and middle third of the media.
- MC site = along the **right lateral wall of the ascending aorta** where the **shear stress is high**; it is NOT usually associated with marked dilation of the aorta.
- Predisposing factors:
 - **Systemic hypertension** (70%) and
 - **Cystic medial necrosis—Erdheim’s disease** (more common in Marfan’s and Ehlers Danlos syn.. type IV).

DeBakey’s classification

- **Type I**—dissection involves ascending to descending aorta.
- **Type II**—limited to ascending and transverse aorta without descending aorta.
- **Type III**—dissection involves descending aorta only.

Stanford classification

- Type A involves ascending aorta (DeBakey I and II) and
- Type B does not (DeBakey III).

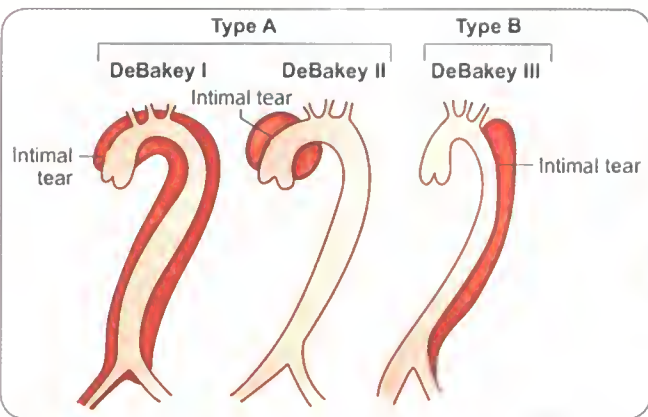


Fig. 21.27: Classification of aortic dissections. Type A (proximal) involves the ascending aorta (DeBakey I and II). Type B (distal or DeBakey III) dissections arise beyond the subclavian artery

- Severe **persistent chest pain of sudden onset** radiating down the **back or to neck** and possibly into the anterior chest.

- The patient is usually **hypertensive**; **Peripheral pulses** may be **diminished or unequal**.
- A **diastolic murmur** may develop due to causing valvular regurgitation, heart failure, and cardiac tamponade.
- Classically, **inferior wall abnormalities** predominate
- A contrast enhanced **multiplanar CT scan** is the **Inv of choice**; MRI is an excellent imaging modality for **chronic dissections**, BUT in the acute situation, the longer imaging time and the difficulty of monitoring patients in the MRI scanner make **the CT scan preferable**.
- **Urgent reduction of BP** and **urgent surgical intervention** required.

HYPERTENSION

Blood Pressure Classification

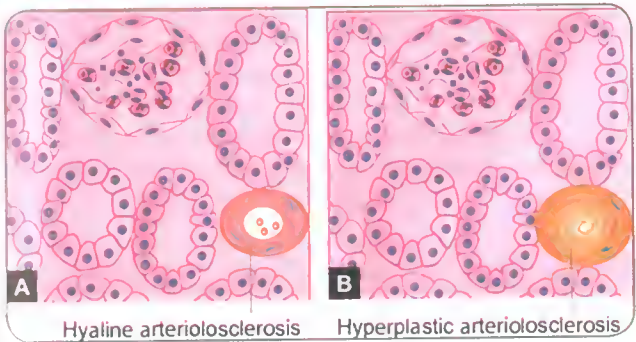
Category	Systolic BP	Diastolic BP
Normal	< 130	> 85
High normal	130–139	85–90
Hypertension		
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	> 180	> 110

Risk Factors for Hypertension (PSM Aspects)

Non modifiable	Modifiable
<ul style="list-style-type: none">• Age• Sex• Genetic factors• Ethnicity	<ul style="list-style-type: none">• Obesity• Salt intake• Saturated fat• Dietary fibre• Alcohol• Heart rate• Physical activity• Environmental stress• Socio economic status

Vascular Pathology in Hypertension

Hyaline arteriolosclerosis	Hyperplastic arteriolosclerosis
<ul style="list-style-type: none">• A/w mild diabetes and mild hypertension.• Endothelial injury → migration of circulating monocytes and other inflammatory cells, which engulf lipoproteins and oxidized LDL → production of inflammatory mediators → continued inflammation and build of cholesterol → formation of plaques.	<ul style="list-style-type: none">• Characteristic of malignant hypertension.• Frequently associated with fibrin deposition and wall necrosis (necrotizing arteriolitis)



Figs. 21.28A and B: Vascular changes (in renal blood vessels) in hypertension. A. Hyaline arteriolosclerosis in benign hypertension: The arteriolar wall is thickened, hyalinized, and the lumen is narrowed; B. Hyperplastic arteriolosclerosis in malignant hypertension: Shows onion-skinning with obliteration of arteriolar lumen.

Treatment of hypertension

- Anti hypertensive drugs have been discussed in pharmacology chapter (Pg 330).

CORONARY HEART DISEASE (CHD)

- CHD may manifest itself in many presentations:
 - **Angina pectoris** on effort
 - **Myocardial Infarction**
 - **Irregularities** of the heart
 - **Cardiac failure**
 - **Sudden death**.

Risk factors for CHD

Non-modifiable	Modifiable
<ul style="list-style-type: none">• Age• Sex• Family history• Genetic factors• Personality (?)	<ul style="list-style-type: none">• Cigarette smoking• High BP• Elevated serum cholesterol• Diabetes• Obesity• Sedentary habits• Stress

- Risk of Coronary heart diseases is same as non-smokers **after 15 years** of quitting smoking.
- The **BP is the single most useful test** for identifying individuals at high risk of developing CHD.
- **HDL is protective** against CHD. (“**HDL = Healthy, LDL = Lousy!!**”).
- A **cholesterol/HDL ratio of < 3.5 has been recommended** as a clinical goal for CHD prevention.
- **Primordial prevention**—preventing the emergence of **CHD risk factors and lifestyles** that **have not yet appeared or become endemic**.

- **Framingham study** is a prospective study that established the **nature of CHD risk factors** and their importance.
- **Hypertension** is an ‘iceberg’ disease for which the ‘**rule of halves**’ applies.
- “**Cholesterol/HDL ratio**” recommended for CHD prevention is < 3.5.

‘METABOLIC SYNDROME = SYNDROME X’

- **Metabolic syndrome = Insulin resistance syndrome = Syndrome X = Reaven’s syndrome** = all synonyms.
- Strongly **a/w atherosclerosis** and is manifested by **macrovascular disease (coronary, cerebral, peripheral)** and an **excess mortality**.

Features of the “Metabolic syndrome”

- **Central (visceral) obesity** (Waist circumference >102 cm (Males), >88 cm (Females); **HIGH waist: hip ratio**
- (Waist: Hip ratio > **1.0 in men and > 0.85 in women** indicates **abdominal fat accumulation**)
- Hyperinsulinemia
- Type 2 diabetes mellitus or impaired glucose tolerance
- **Low HDL cholesterol:** <40 mg/dL and <50 mg/dL, respectively, or specific medication **Hypertriglyceridemia:** Triglycerides ≥150 mg/dL or specific medication
- **Hypertension** (Blood pressure ≥130 mm systolic or ≥85 mm diastolic or specific medication)
- Microalbuminuria
- Increased fibrinogen
- Increased plasminogen activator inhibitor-1
- Increased sympathetic neural activity
- Elevated plasma uric acid

CARDIOPULMONARY BYPASS GRAFTING

- **Cardiopulmonary bypass** was first used by **Gibbon** in 1953.
- MC surgical approach to the heart is by **median sternotomy**.
- The left anterior descending (**LAD**) **coronary artery** (branch of left coronary artery) is the **MC diseased** coronary artery and most often bypassed during CABG surgery.
- The question of **anatomical dominance** is determined by the **artery that supplies the posterior descending artery**. In approximately 90 per cent of cases, the **posterior descending artery arises from the RCA**, a pattern referred to as ‘**right dominance**’.
- **Coronary angiography remains gold standard** for imaging coronary artery anatomy.

- Any **stenosis** in an artery of **>70 per cent** of the diameter (90 per cent reduction on cross-sectional area) is considered 'severe'.
- For CABG, **left Internal mammary artery (LIMA)** is the **conduit of choice** since **ten-year patency rates are 90%**; compared to 50% for vein grafts.
- Second alternative** is **radial artery**.
- When vein is used, **long saphenous vein** is the **MC vein** used.
- Superb exposure of the heart and the great vessels has made the **median sternotomy** incision the **gold standard** for cardiac surgery, particularly for CABG.
- The **MC postoperative arrhythmia** following CABG is **sinus tachycardia** followed by atrial fibrillation.
- PARSONNET** and **EuroSCORE** are scoring systems used for **risk stratification of cardiac surgery**.
- Minimally invasive direct coronary artery bypass = **MIDCAB**.
- Indications for CABG (a/w improved survival post-op)**
 - 50% stenosis of left main stem ('critical left main stem disease')
 - 70% stenosis of the proximal left anterior interventricular artery
 - All 3 main coronary arteries diseased ('triple vessel disease')
 - Poor ventricular function a/w coronary artery disease.

HEART TUMORS

Myxoma of Heart

- MC primary cardiac tumor** in adults.
- MC clinical presentation** is that of **mitral valve disease**.
- Two types of myxoma are:
 - Sporadic myxoma**—solitary, **MC in left atrium**. Cause ball-valve obstruction, embolism, fever.
 - Familial or syndrome myxomas (AD)** tend to occur in younger individuals, **multiple** in location, pedunculated and tend to have postoperative recurrences.
- Myxoma associated syndromes are:
 - NAME syn.**—Nevi, Atrial myxoma, Myxoid neurofibroma, Ephelides.
 - LAMB syn.**—Lentigenes, Atrial Myxoma, Blue nevi.
 - Carney syn.**—multiple myxomas (usually right atrial), lentofacial freckling ± Cushing's, acromegaly or Sertoli cell tumor.

Other Heart Tumours

- Rhabdomyomas**—**MC** primary heart tumor in **children**; often a/w **tuberous sclerosis**; composed of **spider cells** and **glycogen vacuoles**.
- Lipomas**—**MC** in **left ventricle**.
- Papillary fibroelastomas**—Incidental finding at **autopsy**. Found on right-sided valves in children and left-sided valves in adults.
- Metastases (secondaries)** in the heart arise **MC** from **malignant melanoma**.

CARDIAC CATHETERIZATION

- Cardiac catheterization** and angiography remain the **gold standard** for the assessment of both **anatomy and physiology of the heart** and vasculature.
- Werner Forssmann** first applied cardiac catheterization to humans in 1929.
- Andre Cournaud and Dickinson Richards** in New York shared the **Nobel Prize** with **Forssmann** in 1956.
- Most (>95%) cardiac catheterizations** are performed by the **percutaneous femoral technique** that begins with needle puncture of the **common femoral artery**—**Seldinger technique**.
- The normal left ventricle ejects 50 to 80 percent of its end-diastolic volume with each beat; i.e., its **ejection fraction** is **0.50 to 0.80**.
- "Square root" sign** on right ventricular pressure tracing is seen in **constrictive pericarditis**.
- Nonsynchronous contraction (**Mechanical dyssynchrony**)—adversely affects ventricular filling; evidenced by **widened QRS + LBBB** pattern; resynchronization therapy with biventricular pacing is indicated when **EF of <= 35%, and QRS duration >= 120 milliseconds**.
- The **Gorlin equation** is used to **calculate mitral or aortic valve area** during invasive hemodynamic assessment via cardiac catheterization.

PULSELESS ELECTRICAL ACTIVITY

- Pulseless electrical activity**, also called **electromechanical dissociation** is the condition in which **peripheral pulses are not palpable** BUT heart shows **some electrical activity on ECG** other than ventricular tachycardia and ventricular fibrillation.
- Causes are:

"4 Ts"	"4 Hs"
<ul style="list-style-type: none">Tension pneumothorax,Cardiac Tamponade,Pulmonary Thromboembolism,Toxins (beta blockers, calcium channel blockers, digitalis)	<ul style="list-style-type: none">Hypoxia,Hypovolemia,Hypothermia,Hypokalemia

MORE ONE-LINERS

- In **aortic stenosis**, **surgical correction is recommended** when the peak systolic gradient across the aortic valve is greater than 50 mmHg or with a **valve area less than 0.7 sq.cm**.
- Normal mitral valve area** is **4-6 sq.cm**. In severe stenosis valve is reduced to 1-1.5sq.cm.
- MC involved chamber** in **penetrating injury to the heart is the right ventricle**.
- MC congenital heart disease** = **VSD**.
- Pentalogy of Fallot** = **Tetralogy + ASD**.
- Total correction of tetralogy of Fallot** is undertaken **after the age of 2 years**.
- Operative procedures for TGA include atrial inversion (**Senning or Mustard operation**) and arterial switch (**Jatene operation**).
- Thrombus formation** remains the **MC complication** of mechanical and biological **prosthetic valves**.
- MC cardiac manifestation of SLE and Rheumatoid arthritis** is **pericarditis**.
- SLE in mother** can cause **congenital complete heart block** in child (? due to damage by maternal IgG).
- Thiamine (B1) deficiency (Beri beri)** can cause **High-output failure**, dilated cardiomyopathy
- Hyperhomocysteinemia** can cause **Premature atherosclerosis**
- Commotio cordis** is a blunt trauma to chest which may trigger ventricular fibrillation in adolescents during sports injury.
- Dallas criteria**: Histological classification of **viral myocarditis**.

PRE-OPERATIVE CARDIAC RISK ASSESSMENT

- A number of scoring systems (as below) have been developed over the years with the aim of identifying high-risk patients, preoperatively itself.
- ASA** (American Society of Anesthesiologists, see anesthesia chapter) is simple, but subject to user interpretation.

- MET** (Metabolic equivalent of task, see box below) measures exercise tolerance related to daily living.
- RCRI** of Lee (Revised Cardiac Risk Index, see table below) used to predict cardiac risk for non-cardiac surgery.
- POSSUM** (Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity) can only be used postoperatively and better for some types of surgery, e.g. colorectal, vascular.
- CPET** (cardiopulmonary exercise testing) is non-invasive, objective and becoming increasingly popular.

Metabolic Equivalent of Task (MET)

- 1 MET = 3.5 mL O2/kg per minute (oxygen consumption by 40 year, 70 kg man at rest)
- 1 MET = eating and dressing
- 4 MET = climbing two flights of stairs
- 6 MET = short run
- >10 MET = able to participate in strenuous sport
- Patients who can exercise at 4 METS or above have lower risk of peri-operative mortality

Revised Cardiac Risk Index

Independent Predictors of Postoperative Cardiac Complications	
<ol style="list-style-type: none">Intrathoracic, Intraabdominal or suprainguinal vascular surgeryHistory of Ischemic heart diseaseHistory of heart failureInsulin treatment for Diabetes MellitusSerum Creatinine Level > 2 md/dLHistory of cerebrovascular disease	
Scoring (number of predictors present)	Risk of major cardiac complications
None	0.4 %
1	1 %
2	2.4 %
3 or > 3	5.4 %

Note

- For Cardiac Radiology: See Radiodiagnosis chapter (Pg 1176)
- For Congenital Heart disease: See Pediatrics chapter (Pg 674)

GASTROINTESTINAL SYSTEM

MALABSORPTION SYNDROMES

- All can cause *diarrhea, steatorrhea, weight loss, nutritional deficiencies and weakness.*
- Details of each disorder given below.

Tropical Sprue

- Seen in *tropics—West Indies mainly, also in south India, Malaysia and Indonesia.*
- A/w *folate deficiency.*
- **Pathology:** Resembles celiac disease; affects *entire small bowel; partial villous atrophy* is more common.
- **Treatment:** *Tetracycline, 250 mg QID for 28 days* is the *treatment of choice* and brings about long term remission or cure + *Folic acid* replacement.

Celiac sprue (Gluten Sensitive Enteropathy)

- Genetic disorder (A/w *HLA-DQ2 MC*) of *gluten* (e.g., *wheat, barley, rye*) intolerance.
- **IgA antiendomysial; Anti-tissue transglutaminase (tTGA) and antigliadin** (gliadin = *wheat*) **antibodies** cause *jejunal mucosal damage.*
- Occurs *within the 1st year* or in *third decade* of life; MC in *northern Europe.*
- Proximal small bowel — jejunum affected — jejunal biopsy demonstrates loss of duodenal and jejunal villi, *lymphocytes in lamina propria.*
- Serum levels of *tissue transglutaminase* are used for screening.
- A/w *dermatitis herpetiformis.* Moderately ↑ risk of malignancy (*T cell lymphoma*).
- Treatment: A *gluten-free diet* (histology reverts to normal!).

- Whipple's disease**
- Due to *Tropheryma whippell* infection.
 - **PAS positive foamy macrophages** in intestinal lamina propria.
 - Arthralgias, cardiac and neurologic symptoms are common.
 - Most often occurs in *older men.*
 - Treatment: **TMP-SMX or ceftriaxone** for 12 months.

- Lactase deficiency**
- **Intolerance to milk/milk products** ingestion. **NORMAL** appearing villi.
 - Positive **lactose breath test** (i.e., increased hydrogen concentration in expired air following a lactose meal); positive lactose tolerance test (i.e., minimal increase in serum glucose concentration following a lactose meal).

- Pancreatic insufficiency**
- Due to cystic fibrosis, obstructing cancer and pancreatitis.
 - Causes *malabsorption of protein, fat and vitamin A, D, E, K.*

Tests for Malabsorption

- **Schilling Test:**
 - Performed to determine the cause for *cobalamin malabsorption.*
 - Since cobalamin absorption requires multiple steps, including gastric, pancreatic, and ileal processes, the Schilling test can also be used to assess the integrity of these other organs.
 - Schilling test is **abnormal** in:
 - **Pernicious meinin**
 - Chronic pancreatitis
 - Achlorhydria
 - Bacterial overgrowth syndromes
 - **Ileal dysfunction**
- **Small bowel study:**
 - Radiologic examination of the *small intestine* using **barium contrast (Small-bowel barium enema enteroclysis)** remains a useful examination to look for *anatomical abnormalities*, such as
 - Strictures and fistulas (as in Crohn's disease) or
 - Blind loop syndrome (e.g., multiple jejunal diverticula),
 - To define the extent of a previous surgical resection
- **Biopsy:**
 - Small-intestinal mucosal biopsy is *essential* in the evaluation of a patient with documented *steatorrhea or chronic diarrhea* (lasting >3 weeks).
- **Urinary D-xylose test**
 - For carbohydrate absorption provides an assessment of proximal *small-intestinal mucosal function.*

Disorders in which Small Bowel Biopsy has Diagnostic Value

- **Whipple's disease:** Lamina propria infiltrated with macrophages containing **PAS positive granules.** Cause by gram-negative actinomycete ***Tropheryma whippell***.
- **Abetalipoproteinemia:** Villous structure normal, epithelial cells vacuolated due to excess fat.
- **Agammaglobulinemia:** Flattened or absent villi, increased lymphocyte infiltration, absence of plasma cells, hypoplastic Peyer patches.
- ***Mycobacterium avium* complex:** Infiltration of villi by histiocytes loaded with acid fast bacilli.
- **Amyloidosis:** Amyloid in the small bowel stained with Congo red.
- **Intestinal Lymphoma**
- **Eosinophilic gastroenteritis**
- **Crohn's disease**
- **Mastocytosis**
- **Tropical and celiac sprue.**

ACUTE DIARRHEAS

Organisms	Clinical features and treatment
1 to 6 hours incubation period	
<i>Staphylococcus aureus</i>	<ul style="list-style-type: none"> • <i>Staphylococci</i> grow in meats, dairy and bakery products (room temperature food) and produce enterotoxin (preformed toxin). Nausea, vomiting first, diarrhea later. • No treatment usually necessary except to restore fluids and electrolytes.
<i>Bacillus cereus</i>	<ul style="list-style-type: none"> • Emetic form – MC; Reheated fried rice (preformed toxins) cause nausea, vomiting first, diarrhea later; fever is rare. • Self limited to less than 1 day.
8 to 16 hours incubation period	
<i>Clostridium perfringens</i>	<ul style="list-style-type: none"> • <i>Clostridia</i> grow in rewarmed meat dishes and produce enterotoxin (preformed toxins). • Abdominal cramps, diarrhea (vomiting, fever are rare). • Recover usually without treatment in 1–4 days.
<i>Bacillus cereus</i>	<ul style="list-style-type: none"> • Enterotoxin in small intestine OR Preformed toxins in meat vegetables, dried beans, cereals. • Diarrheal form: Abdominal cramps, diarrhea (vomiting, fever rare). • Self limited to less than 1 day.
> 16 hours incubation period	
<i>Salmonella</i>	<ul style="list-style-type: none"> • Due to ingestion of milk and egg products, sausages, custard. • Organisms grow in gut, do not produce toxin. • Infective dose is 10⁵ organisms. • Watery diarrhea with low-grade fever. • No antibiotics unless systemic dissemination is suspected, in which case give a fluoroquinolone. • Stool cultures are positive, prolonged carriage is common.
<i>Vibrio cholerae</i>	<ul style="list-style-type: none"> • Due to ingestion of shellfish. • Organisms grow in gut and produce enterotoxin, which causes hypersecretion in small intestine (watery diarrhea). • Infective dose is 10³–10⁶ organisms. • Needs prompt replacement of fluids and electrolytes IV or orally. • Tetracyclines shorten excretion of vibrios. • Stool cultures positive.
<i>Enterotoxigenic E. coli</i>	<ul style="list-style-type: none"> • Due to ingestion of salads, cheese, meat, water. • Organisms grow in gut and produce toxin. Abrupt onset of watery diarrhea. • In adults 'traveller's diarrhea' is self limited to 1–3 days and does respond to a fluoroquinolone.
<i>Shigella</i>	<ul style="list-style-type: none"> • Due to ingestion of potato or egg salad, lettuce, raw vegetables. • Causes bloody diarrhea/dysentery, fever. • Organisms invade epithelial cells; blood mucus and PMNs in stools. • Infective dose is low: 100–1000 organisms. • Risk of HUS present. • TMP-SMX in severe cases.
<i>Vibrio parahaemolyticus</i>	<ul style="list-style-type: none"> • Organisms grow in seafood and molluscs and in gut and produce toxin or invade. • Cause dysentery. Recovery is usually complete in 1–3 days.
<i>Clostridium botulinum</i>	<ul style="list-style-type: none"> • Organisms produce toxin (preformed toxin) in home canned foods, honey. • Botulism - affects parasympathetic nervous system, gastrointestinal symptoms are minimum. Dysphagia, diplopia, ptosis, dysarthria muscle weakness, even quadriplegia. Frequently fatal in 4–8 days due to cardiac or respiratory failure. Treatment requires clear airway, ventilation, polyvalent antiserum.

EXTRA EDGE

- Causes of invasive diarrhea are: Shigella; EHEC, E. coli 0157:H7; Campylobacter jejuni; Yersinia; Vibrio parahemolyticus.

Food and Disease

Food source	Associated disease
Unpasteurized milk, cheese, ice cream	Brucellosis
Eggs, poultry, beef	Salmonella and non typhoid salmonellosis
Honey	Infant Botulism (intestinal botulism)
Contaminated fried rice, freshly made vanilla sauce	Bacillus cereus food poisoning (emetic form)
Shellfish	Vibrio cholerae food poisoning
Poultry, Potato or egg salad, Mayonnaise, Cream pastries	Staphylococcus aureus food poisoning
Incompletely cooked meat and rice	Cl. perfringens food poisoning
Contaminated milk products, chicken	C. jejuni

Few Other Infectious Diarrheas

- C. jejuni: Due to **poultry** ingestion, bloody diarrhea, fever; risk of **Gullain Barre syndrome** present.
- EHEC, E.Coli 0157:H7: Ingestion of round beef, **direct fecal contamination**; bloody diarrhea, vomiting, fever, abdominal pain, risk of **Hemolytic Uremic syndrome** (HUS).

INFLAMMATORY BOWEL DISEASE

Crohn's Disease and Ulcerative Colitis Compared

	Crohn's disease (CD)	Ulcerative colitis (UC)
Site of involvement	Entire GI tract may be involved (mouth to anus) with "skip" areas Distal ileum MC involved; Rectum often spared A.k.a regional enteritis	Continuous disease beginning at rectum and extending possibly as far as distal ileum Rectum always involved
Pathology	All layers of bowel wall involved (transmural) <i>Granulomas</i> ; <i>Creeping fat</i>	Only mucosa and submucosa affected (mucosal) Crypt abscesses
Symptoms	Watery diarrhea Abdominal pain, weight loss	Bloody diarrhea Abdominal pain, urgency, tenesmus, weight loss, nausea, vomiting
Clinically	Palpable right lower quadrant abdominal mass Perianal fissures and fistula Aphthaus ulcers (earliest microscopic feature) Fever	Fever, Abdominal tenderness, Orthostatic hypotension, tachycardia, gross rectal bleeding

- Y. enterocolitica: Due to **Pork** ingestion: Bloody diarrhea, **right lower quadrant pain**.

Chronic Diarrheas

Type	Cues	Examples
Secretory diarrheas	↑↑ stool volume (> 1L/d); little change with fasting, normal stool osmotic gap.	Carcinoid syn., Zollinger-Ellison syn., VIPomas, medullary thyroid carcinoma, villous adenoma of rectum, microscopic colitis, cholerrheic diarrhea
Osmatic diarrheas	Stool volume ↓ with fasting, ↑ staal osmatic gap.	Abetalipoproteinemia, bacterial overgrowth, celiac sprue, lactase deficiency, pancreatic insufficiency, short bowel syn., Whipple's disease
Inflammatory diarrheas	Fever, hematochezia, abdominal pain	Crohn's disease, ulcerative colitis, radiation enterocolitis, eosinophilic gastroenteritis, infections a/w AIDS, malignancy (lymphoma, adenocarcinoma)
Diarrheas due to altered intestinal motility	Systemic diseases or prior abdominal surgery	Irritable bowel syn., fecal impaction, neurologic diseases, systemic diseases (scleroderma, DM, hyperthyroidism)

Contd...

Contd...

	Crohn's disease (CD)	Ulcerative colitis (UC)
Labs	3X more risk in smokers ASCA frequently positive, pANCA rarely positive <i>Hemocult positive stool</i> Biopsy diagnostic	Smoking is protective !! ASCA rarely positive, pANCA frequently positive Biopsy diagnostic
Radialagy	Skip lesions , Colonic ulcers Cobble stoning mucosa Strictures 'String sign of Kantor" and Comb sign on Ba swallow	Continuous involvement Fine mucosal ulcers (double contour) Pseudopolyps, friable mucosa 'Lead pipe Comb sign' colon without haustra and colon shortening
Camplications	Abscess formation Fistula , fissure and strictures common Malabsorption (since ileal disease)	Increased risk of colan cancer Hemorrhage Bowel obstruction Toxic megacolon

S-I-M To remember features of Crohn's disease you could imagine:

- "**2 absessed** (abscesses) **fish** (fissures and fistulas) **skipping** (skip lesions) on a **cabblestoned** (cobblestones) path **fully penetrated** (transmural) **fat** (creeping fat) **grandma's** (granuloma) house wall. She caught them with a **string** (strictures, String sign) and ate them and got **ulcers at bath ends** (mouth and perianal), and screamed '**AMMA**' (Abdominal Mass and **MA**labsorption)"

ASCA = Antiyeast saccharomyces cerevisiae antibodies.

Extraintestinal Manifestations of Inflammatory Bowel Disease

Related to disease activity	Unrelated to disease activity
<ul style="list-style-type: none">Erythema nodosumArthropathy (asymmetrical)Conjunctivitis, episcleritis, uveitisThrombo-embolic diseaseAmyloidosisPyoderma Gangrenosum (more common in UC)Gallstones (not in UC)Bile salt deficiency with ileal disease (increased colonic oxalate absorption leading to renal stones, increased lithogenecity of bile leading to gallstones)	<ul style="list-style-type: none">SacroiliitisAnkylosing spondylitisPrimary Sclerosing Cholangitis (more common in UC)

Mnemonic: "**Pretty Girls and Sweet Chicks are more common in University of California**".

Treatment of IBD

- 5-ASA (5-AminoSailicylicAcid) derivatives
➤ **Mesalamine**

- Azo compounds: **Sulfasalazine**, Olsalazine, Balsalazide
- Corticosteroids
- Immunomodulating drugs: Mercaptopurine, Methotrexate and Azathioprine.
- Biologic therapy
 - **Anti-TNF** drugs: Infliximab, Adalimumab; Golimumab; Certolizumab
 - **Anti-integrins**: Natalizumab (risk of PML due to JC virus reactivation); **Vedolizumab**.
- Surgical resection of severely affected areas; surgery for toxic megacolon.

EXTRA EDGE

- Mutations in **NOD2/CARD15 genes** are a/w **Crahn's disease**; other genes are **ATG116L1** and **IRGM**.
- '**Metastatic**' **Crahn's disease** can occur in the **vagina or skin** with nodular ulcers, which demonstrate non-caseating granulomas when biopsied.
- Infection with *Campylobacter jejuni* and *amoebiasis* can resemble *Ulcerative Colitis*.
- Yersinia enterocolitica* can cause a granulomatous inflammatory process that mimics *Crohn's disease*.

CENTRAL NERVOUS SYSTEM

PATHOLOGY

Neuroglia

Neuroglial cell	Location	Function	Comments
Astrocytes			
Fibrous	White matter	Provide supporting framework , are electrical insulators, limit spread of neurotransmitters, take up K ⁺ ions	Astrocyte marker – GFAP
Protoplasmic	Grey matter	Store glycogen, take place of dead neurons – i.e. reactive gliosis in response to injury	
Oligodendrocytes	In rows along myelinated nerves surrounding cell bodies – white matter	Form myelin in CNS , influence biochemistry of neurons	These cells are destroyed in multiple sclerosis
Microglia	Scattered throughout CNS	Are inactive in normal CNS, proliferate in disease and phagocytosis together with blood monocytes, Gitter cells	Phagocytes of CNS . Like Macrophages originate from Mesoderm
Ependyma			
Choroidal epithelial cells	Cover surfaces of choroidal plexus	Produce and secrete CSF	
Ependymocytes	Line ventricles, central canal	Circulate CSF, absorb CSF	
Tanycytes	Line floor of third ventricle	Transport substances from CSF to hypophyseal portal system	

Cerebral Edema

Vasogenic edema	<ul style="list-style-type: none">Primarily affects white matter.Seen with trauma, tumors, toxicity (lead) and infections.Results from increased permeability of capillary endothelial cells (i.e. breakdown of blood brain barrier)MC clinically seen type
Cytotoxic edema	<ul style="list-style-type: none">Primarily affects grey matter.Is equivalent to hydropic cell swelling (accumulation of intracellular water)Seen within minutes after an insult, such as ischemia/hypoxia.Vascular permeability is unaltered.
Interstitial edema	<ul style="list-style-type: none">Is seen in hydrocephalus.Fluid accumulates in the cerebral ventricles and periventricular white matter.

- Signs: CN III palsy (dilated pupil, oculomotor palsy); contralateral homonymous hemianopia (compression of posterior cerebral A); ipsilateral paresis (compression of contralateral crus cerebri) (**Kernohan's notch, Kernohan-Woltman sign**) – false localizing sign; **Duret hemorrhages** (paramedian A rupture leading to delayed upper brainstem hemorrhage), caudal displacement of brainstem
- **Subfalcine (cingulate) herniation:**
 - Compromise of anterior cerebral A branches
- **Tonsillar:**
 - Displacement of cerebellar tonsil into foramen magnum

Hydrocephalus

Noncommunicating	Local enlargement of one or more ventricles secondary to an obstruction within the ventricular system , most often the aqueduct or the foramen of Monro.
-------------------------	---

Contd...

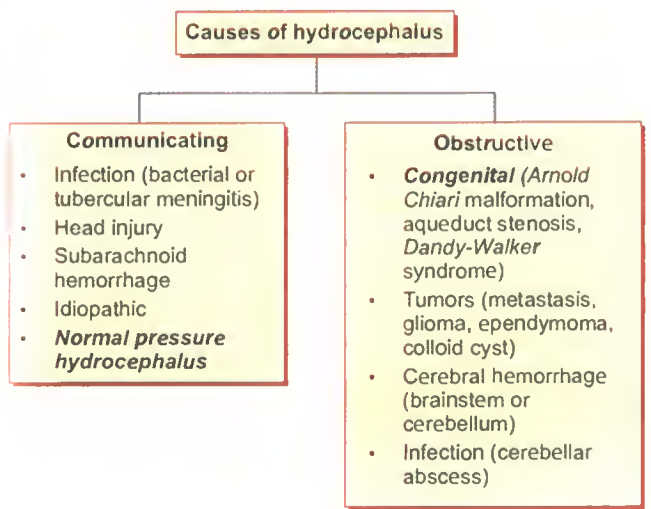
Brain Herniations

- **Transtentorial (Uncal) herniation (MC type):**
 - Compression of medial temporal lobe leads to herniation of tentorium cerebelli.

Contd...

Communicating	Enlargement of the entire ventricular system secondary to an obstruction outside the system usually in the subarachnoid space or arachnoid granulations
Hydrocephalus ex vacuo	Dilatation of ventricles secondary to atrophy of parenchyma
Normal pressure hydrocephalus	Consists of a clinical triad of abnormal gait (ataxic or apractic), dementia , and urinary incontinence . It is a type of communicating hydrocephalus with a patent aqueduct of Sylvius; periventricular edema is present; Enlarged lateral ventricles (hydrocephalus) with LITTLE OR NO cortical atrophy on CT/MRI

- **MC shunt for hydrocephalus is ventriculoperitoneal shunt.**



Primary and Secondary Brain Injury

Primary brain Injury	Secondary brain Injury
<ul style="list-style-type: none">• Injury to the brain and associated structures that results instantaneously from impact to the head. Example: Coup and Contrecoup injuries	<ul style="list-style-type: none">• Physiologic impairments that result from the primary injury. Example: Cerebral edema, increased ICP, ischemia, hypoxia and infection.• Secondary brain injuries are potentially preventable.

Brain Parenchymal Injuries

Concussion	Contusion
<ul style="list-style-type: none">• A transient neurologic syndrome occurring after trauma with brief loss of consciousness, respiratory arrest and loss of reflexes. Amnesia for the event persists.• It is not a/w permanent brain damage.	<ul style="list-style-type: none">• Bruises of crests/gyri showing microscopically hemorrhages.• After resolution, a depressed, yellowish scar extends to the pial surface (plaque jaune).

MIGRAINE

Diagnostic Criteria for Migraine

Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:	
AT LEAST 2 of the following features:	PLUS at least 1 of the following features:
<ul style="list-style-type: none">• Unilateral pain• Throbbing pain• Aggravation by movement• Moderate or severe intensity	<ul style="list-style-type: none">• Nausea/vomiting• Photophobia and phonophobia

Migraine Classification

Migraine with Aura

- **Aura < 60 min** and typical, full recovery.
- Severe **hemicranial throbbing or pulsatile pain** with aura consists of **scintillating scotoma, zig zag rays** of various colors called **fortification spectra (teichopsia)**
- **Migraine with prolonged aura**
- **Aura > 60 min**, full recovery

Ophthalmoplegic Migraine

- **Transient paresis** of III, IV or VI occurring during migraine and lasting for days-weeks, usually full recovery, rare

Basilar Migraine

- Bilateral visual disturbance + brainstem/cerebellar aura (**collapse, diplopia, vertigo, dysarthria, ataxia**)

Retinal Migraine

- **Recurrent monocular visual disturbance**, variable scotoma (dark/light/scintillating; focal/altitudinal/complete), 5–15 min duration, retinal vessels narrowing during attack

Familial Hemiplegic Migraine

- Familial, AD, hemiparesis +/- sensory/visual/speech/cerebellar aura; rare

Migraine Aura Without Headache

- **Acephalgic migraine**, MC over 40 years, must be differentiated from TIAs.

Other Headaches

Cluster headache	Severe unilateral, retro-orbital headache in clusters several times daily for several days or weeks; a/w ipsilateral lacrimation, rhinorrhea, nasal and ocular congestion and Horner syndrome; more at night and with alcohol . Treatment of choice for acute attack of cluster headache is 100% oxygen at 10–12 L/min for 15–20 min.
Tension headache	MC primary headache disorder ; Non-throbbing bilateral occipital head pain that is described as tight band around the head.
Thunderclap headache	Acute severe headache (subarachnoid hemorrhage)
Brain tumor	<i>Disturbs sleep</i> , unrelieved by sleep. Steadily worsening dull pain, worsens with exertion or change in position , may be preceded by days/weeks of nausea and vomiting.
Giant cell arteritis	Temporal pain , > 55 years, scalp tenderness, intermittent throbbing, jaw claudication , ↑ ESR, fever, polymyalgia rheumatica
Lumbar puncture headache	In patients > 10 years of age; bifrontal and/or bioccipital; orthostatic headache present in sitting/standing position and disappears in prone/supine positions

Treatment of Migraine

- Analgesic/NSAIDs
 - Aspirin, PCT, ibuprofen, diclofenac, tolifenamic acid or naproxen
- 5HT₁-1 receptor agonist
 - **Cafergo**, a combination of **ergotamine tartrate** and **caffeine** (avoid ergot in pregnancy and CVS disease)
- Dopamine receptor antagonist
 - **Prochlorperazine, Metoclopramide**
- 5HT_{1D/1B} agonist
 - **Triptans** (sumatriptan, zolmitriptan, etc.)—oral, nasal or SC
- **Lasmiditan** (5HT_{1F} receptor agonist) and **Oliceridine** (Calcitonin Gene-Related Peptide - CGRP antagonist) are in clinical trials.

Prophylaxis of Migraine

- **Beta blockers** (Propranolol; Timolol)
- **Anti-depressants** (Amitriptyline, venlafaxine)
- **Anti-convulsants** (Topiramate, Valproic acid)
- **Serotonergic drug** (Methysergide)
- **Candesartan** (Angiotensin receptor blocker)
- Ona **Botulinum toxin A**
- **Flunarizine, Pizotifen, Methysergide**

EXTRA EDGE

- NO convincing evidence from controlled trials: Verapamil
- Controlled trials demonstrate NO effect: Nimodipine, Clonidine, SSRIs (fluoxetine).
- **MIDAS = Migraine Disability Assessment Score.**

STROKE

Basics

- A decrease in cerebral blood flow to **zero** causes death of brain tissue within **4–10 min**; values **<16–18 mL/100 g** tissue per minute cause infarction **within an hour**; and values **<20 mL/100 g** tissue per minute cause ischemia without infarction unless prolonged for several hours in days.
- **Ischemic penumbra**, defined as the **ischemic but reversibly dysfunctional tissue** surrounding a core area of infarction. The penumbra can be imaged by **perfusion-diffusion imaging** using MRI or CT
- **Saving the ischemic penumbra** is the **goal of revascularization** therapies.

Types of Stroke

- **Acute ischemic stroke (MC type, 85%)**. It is of two types:
 - Acute ischemic **thrombotic** stroke (**MC type, 80%**; MC due to **atherosclerosis**).
 - Acute ischemic **cardioembolic** stroke (**Second MC type, 20%**; MC due to nonrheumatic **atrial fibrillation**).
- **Acute hemorrhagic stroke (15%)**
 - **MC cause of hemorrhagic stroke is uncontrolled hypertension.**
- **Paradoxical embolization** occurs when **venous thrombi migrate to the arterial circulation**, usually via a **patent foramen ovale or atrial septal defect**. **Bubble-contrast echocardiography** (IV injection of agitated saline coupled with either transthoracic or transesophageal echocardiography) can demonstrate a right-to-left cardiac shunt, revealing the conduit for paradoxical embolization.

- The term 'small-vessel stroke' (lacunar infarction) denotes occlusion of a small penetrating artery in the brain. Small-vessel strokes account for ~20% of all strokes.
- The risk of stroke in nonrheumatic atrial fibrillation can be estimated by calculating the CHADS score as below:
 - Congestive heart failure history, 1 point
 - Hypertension history, 1 point
 - Age > 75 years, 1 point
 - Diabetes mellitus history, 1 point, and
 - Stroke or TIA symptoms previously, 2 points

Treatment of Stroke

- 1 Medical support
 - 2 IV thrombolysis (within the '**window period**' of **4.5 hours**)
 - 3 Endovascular revascularization
 - 4 Antithrombotic treatment
 - 5 Neuroprotection, and
 - 6 Stroke centers and rehabilitation.
- **Aspirin** is the **ONLY** antiplatelet agent that has been proven **effective** for the **acute treatment** of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke.
 - Numerous clinical trials have **failed** to demonstrate any benefit of **anticoagulation** in the **primary treatment of atherothrombotic cerebral ischemia**.
 - Several trials have shown that **anticoagulation** (INR range, 2–3) in patients with **chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAf)** **prevents cerebral embolism** and stroke and is safe.

Contraindications for IV rtPA for Acute Ischemic Stroke

- Sustained BP >185/110 mm Hg despite treatment
- Platelets < 100,000; HCT < 25%; glucose < 50 or > 400 mg/dL.
- Use of heparin within 48 h and prolonged PTT, or elevated INR
- Rapidly improving symptoms
- Prior stroke or head injury within 3 months; prior intracranial hemorrhage
- Major surgery in preceding 14 days
- Minor stroke symptoms
- Gastrointestinal bleeding in preceding 21 days
- Recent myocardial infarction
- Coma or stupor

Common Stroke Locations and Corresponding Signs and Symptoms

Location of stroke	Signs and symptoms
Anterior cerebral A	C/L lower limb paralysis and loss of sensation
Middle cerebral A	C/L face and upper limb weakness and ↓ sensation, bilateral visual abnormalities, aphasia (if dominant hemisphere), neglect and inability to perform learned actions (if nondominant hemisphere)
Posterior cerebral A	C/L hemianopia with macular sparing

Location of stroke	Signs and symptoms
Lacunar A	Focal motor or sensory deficits, loss of coordination, difficulty speaking
Basilar A	Cranial nerve abnormalities, C/L full body weakness and ↓ sensation, vertigo, loss of coordination, difficulty speaking, visual abnormalities, coma
Vertebral artery (more commonly) or Posterior Inferior Cerebellar Artery (PICA)	Wollenberg syndrome - Lateral medullary syndrome: vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome.

EXTRA EDGE

- **Diffusion-weighted MRI is gold standard** for identifying acute stroke.

Less common Causes of Stroke

- **Moyamoya disease**: Is an occlusive disease involving **large intracranial arteries**, especially the **distal internal carotid artery and the stem of the MCA and ACA**. Vascular inflammation is **absent**. The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a '**puff of smoke**' (**moyamoya in Japanese**) on conventional X-ray angiography.
- **Posterior reversible encephalopathy syndrome (PRES)** can occur with head injury, seizure, migraine, sympathomimetic drug use, eclampsia, and in the postpartum period.

Contd...

Less common Causes of Stroke

- ▶ **Leukoaraiosis, or periventricular white matter disease.** is the result of *multiple small-vessel infarcts* within the subcortical white matter.
- ▶ **CADASIL** (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an inherited disorder that presents as *small-vessel strokes, progressive dementia, and extensive symmetric white matter changes* often including the anterior temporal lobes visualized by MRI. CADASIL is the **MC hereditary stroke disorder** due to mutation of **NOTCH3** gene on **chromosome 19**.

TRANSIENT ISCHEMIC ATTACKS

- TIAs are episodes of stroke symptoms that last only briefly < **24 h**, but most TIAs last < **1 h**.
- The risk of stroke after a TIA is ~**10-15%** in the **first 3 months**, with most events occurring in the **first 2 days**.
- This risk can be directly estimated using the well-validated **ABCD2 score** as below.
- An ABCD2 score of **4 or more** is a threshold for hospital admission.
- **ABCD2I** = ABCD2 + **I** = 3 points (for any abnormal **I**maging - MRI/CT finding).

Clinical factor	Transient ischemic attack: TIA score
A: Age ≥ 60 years	1
B: SBP > 140 mm Hg or DBP > 90 mm Hg	1
C: Clinical symptoms	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
> 60 min	2
10-59 min	1
D: Diabetes (oral medications or insulin)	1

- Medical treatment is aimed at preventing further attacks of stroke.
- The chief indication for anticoagulation after TIA is atrial fibrillation.
- If anticoagulation is not indicated, antiplatelet therapy should be started.

INTRACRANIAL HEMORRHAGE

Intracerebral Hemorrhage

- Bleeding into **brain substance**
- **MC a/w hypertension**; also seen with amyloid angiopathy, vasculitis, neoplasm.

- MC in **putamen**, basal ganglia) and the adjacent internal capsule is usually damaged
- **Contralateral hemiparesis** is therefore, the sentinel sign.
- There is **lipohyalinosis** of vessel wall, weakening and rupture of **Charcot-Bouchard aneurysms**
- **Non contrast CT scan** superior to MRI for detecting bleeds of < 48 hr duration
- About **40%** of patients with a hypertensive ICH **die**.



Fig. 21.29: Intraparenchymal hemorrhage on the left cerebral hemisphere appears as dark colored area

Epidural vs Subdural hemorrhage

Epidural (extradural) hematoma	Subdural hematoma
Arterial blood accumulates between skull bone and dura	Venous blood accumulates slowly between dura and arachnoid
Rupture of middle meningeal artery (branch of maxillary A) after trauma to temporal bone	Rupture of torn superficial bridging veins between cerebral cortex and sinuses <i>Adults:</i> Trivial head injury, alcoholism epilepsy <i>Children:</i> Birth trauma, child abuse; other trauma
Brief unconsciousness followed by LUCid interval for several hours	Altered consciousness ; pupillary irregularity (ipsilateral to hematoma); hemiparesis (contralateral to hematoma); decerebrate posturing or flaccid motor exam

Contd...

Contd...

Epidural (extradural) hematoma	Subdural hematoma
CT scan: ConvEX mass (<i>lentiform</i>) NOT crossing suture lines "EX tradural = convEX; Always give LUCy EX tra attention!"	CT scan: Concave (<i>crescent-shaped</i>) mass which is less dense than epidural since blood is diluted with CSF; Crosses suture lines

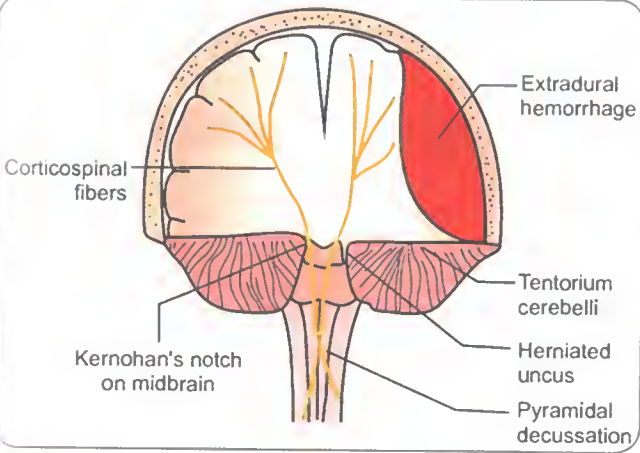


Fig. 21.30: Effects of large extradural hematoma on left side. (Note the herniation of uncus of temporal lobe of cerebrum into the tentorial notch and the shift of midbrain to the right producing compression of corticospinal fibers in the crus of midbrain)

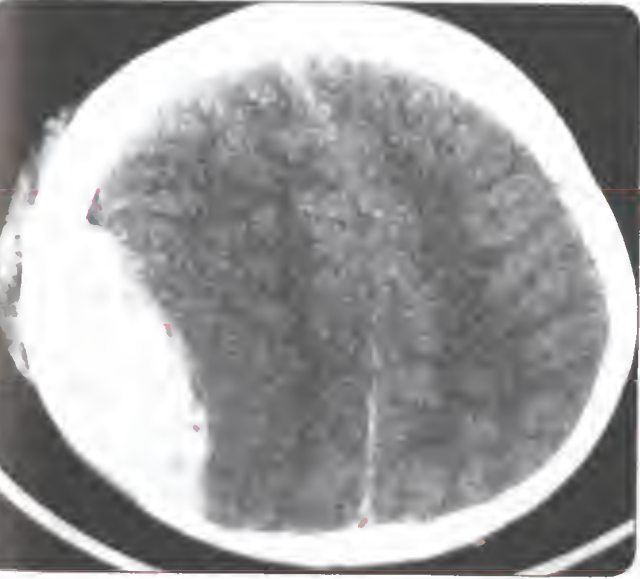


Fig. 21.31: CT scan head showing extradural hematoma with biconvex lesion



Fig. 21.32: CT scan head showing subdural hematoma with concavoconvex lesion

Subarachnoid Hemorrhage

- Bleeding into **subarachnoid space**
- Overall **MC cause** is **trauma**
- **MC** cause of **spontaneous SAH** is rupture of **Berry aneurysm** (seen in Marfan's, Ehlers-Danlos and ADPKD), sudden onset, classically '**worst headache in life**'/**thunderclap** headache;
- **Bloody** or **xanthochromic CSF** on lumbar puncture;
- Treatment with **nimodipine** reduces risk of ischemic injury
- Definitive treatment is **surgical repair** of ruptured aneurysm.
- **Hunt and Hess scale** is for the severity of **non-traumatic SAH**
- **Fischer grading** is the severity of SAH by size (in mm).
- **Non-contrast CT scan** + confirms diagnosis
- Profound **Hyponatremia** may develop quickly following **SAH**.

EXTRA EDGE

- First investigation of choice for **all intracranial hemorrhages** is **noncontrast CT scan**.
- **Acute subdural** hematoma **is ≤ 3 weeks**; chronic is ≥ 3 weeks
- **Chronic subdural** hematoma—signs and symptoms—**Slowed thinking, vague change in personality, headache** (fluctuating in severity with changes in head position), **mild hemiparesis**.

PARKINSON'S DISEASE (PD)

- **First disease** with single neurotransmitter defect identified!
- Loss of *dopaminergic neurons* and **dopamine depletion** in **substantia nigra**, pars compacta and **Lewy body** formation (eosinophilic cytoplasmic inclusions) in substantia nigra neurons leading to abnormally increased inhibition of thalamic-cortical neural pathways.
- May also be due to **MPTP** (methyl-phenyl-tetrahydropyridine) intoxication (contaminant of *illicit opioids*).

Clinical features of Parkinson's disease

- **Bradykinesia** (slow dressing, feeding, writing, walking)
- **Mask like** face (hypomimia)
- **Rigidity (cogwheel)**
- **Rest Tremor** (pill rolling)
- **Shuffling gait** (involuntary gait acceleration after initiation)
- Postural instability
- **Depression**
- **Micrographia** (smaller handwriting compared to earlier)
- Soft voice (hypophonia); reduced eye blinking; dysphagia
- **Myerson sign**: Repetitive tapping over the bridge of the nose produces a sustained blink response

Treatment

- **Anti-Parkinson's drugs**: See *Pharmacology* chapter (Pg 343).
- Surgical treatment of PD – **pallidotomy**, avoided these days since the benefit of this surgery is provided by the noninvasive procedure—deep brain stimulation, itself!
- **Deep brain stimulation**: High-frequency stimulation of the **subthalamic nuclei** (MC site) or **globus pallidus internus** may benefit all the major features of PD.

HUNTINGTON'S DISEASE

- **AD inheritance** characterized by **triplet repeat defects** of **CAG** on **chromosome 4**.
- Causes **genetic anticipation**, **atrophy of caudate nucleus** (loss of GABAergic neurons).
- (**Hunt 4 a date** in a **CAGe** = **Huntington's**, chromosome 4, caudate, CAG triplet).
- **Chorea**, dementia, antisocial behavior.
- MRI: The best known, feature is that of **caudate head atrophy** resulting in **enlargement of the frontal horns**, often giving them a **"box" like configuration**.
- There is **NO** cure for Huntington's disease; progression **cannot** be halted and treatment is purely **symptomatic**.
- **Tetrabenazine**, **reserpine**, **haloperidol** and **amantadine** have been tried.

RESTLESS LEG SYNDROME

- **Causes** of Restless leg syndrome:
 - Idiopathic/familial;
 - Chronic renal failure;
 - Iron-deficiency anemia;
 - Pregnancy;
 - Neuropathy (Diabetic, Peripheral);
 - Multiple sclerosis;
 - Parkinson's disease;
 - Drugs (Caffeine, barbiturates, BZDs, antipsychotics, alcohol);
- Treatment: **Dopaminergic** drugs (pramipexole or ropinirole).

BENIGN ESSENTIAL TREMOR

- Postural tremors of the hand, head or face (**legs** are surprisingly **spared!**)
- **Family history** common; maybe **autosomal dominant**.
- Enhanced by **emotional stress**; Improves temporarily with **alcohol**.
- No treatment required, BUT **propranolol** helps symptomatically.

INHERITED ATAXIAS

- Clinical features of ataxias include gait impairment, unclear ('scanning') speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement.
- These occur due to involvement of the **cerebellum** and its afferent and efferent pathways (**spinocerebellar pathways**, and the **frontopontocerebellar pathway** originating in the rostral frontal lobe).
- The **autosomal dominant** spinocerebellar ataxias (SCAs) include SCA types **1 through 36**.
- **SCA3** is also called **Machado-Joseph** disease.

Classification

- The **autosomal dominant spinocerebellar ataxias** (SCAs) include:
 - SCA types 1 through 36,
 - Dentatorubropallidoluysian atrophy (DRPLA)
 - Episodic ataxia types 1 to 7
 - SCA1, SCA2, **SCA3 (Machado-Joseph disease)**, SCA6, SCA7, and SCA17 are caused by **CAG triplet repeat expansions** in different genes.
 - SCA8 is due to **CTG repeat expansion**,
 - SCA12 is due to **CAG repeat**,
 - SCA10 is caused by an untranslated **pentanucleotide repeat**.

- The clinical phenotypes of these SCAs overlap.
- The genotype has become the gold standard for diagnosis and classification.

Friedreich's ataxia

- Autosomal Recessive
- **MC form** of *inherited ataxia*
- It can occur in a **classic form** or in a/w a genetically determined **vitamin E deficiency** syndrome.
- It presents **before 25 years** of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones.
- The median age of **death is 35 years**.
- **Women** have a significantly better prognosis than men.
- **Cardiac** involvement occurs in **90%** of patients.
- The classic form of Friedreich's ataxia has been mapped to **9q13-q21.1**, and the mutant gene, frataxin, contains expanded **GAA triplet** repeats in the first intron.

AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG DISEASE)

- Chronic degenerative condition involving **motor neurons in the spinal cord**. Caused by defects in **superoxide dismutase 1 (SOD1)**.
- **Sensations and cognition** are **completely intact**.
- A/w **both UMN and LMN signs**:
 - Progressive muscular weakness
 - Generalized muscle atrophy
 - Spasticity
 - Dysarthria
 - Tongue fasciculations
 - Hyperreflexia
 - **Eye movements are spared**
- **EMG** — widespread denervation.
- Treatment:
 - ALS is incurable, progressive disease.
 - **Riluzole** which **inhibits glutamate release** may give modest improvement.

GUILLAIN-BARRE SYNDROME (ACUTE IDIOPATHIC POLYNEURITIS)

- A.k.a. **Acute inflammatory demyelinating polyradiculopathy (AIDP)**, **acute idiopathic polyneuritis**, **Landry's syndrome**, **postinfectious polyneuritis**.
- Recent h/o respiratory or GI infection (**Campylobacter jejuni**).
- Inflammation and demyelination of peripheral nerves and motor fibers of ventral roots – maybe due to **autoimmune attack of peripheral myelin of Schwann cells** due to molecular mimicry.

Tests

- CSF: ↑ **protein with normal WBC levels** ('**albuminocytologic dissociation**')
- Nerve conduction studies show denervation and conduction block.

Clinical

- **Ascending muscle weakness** beginning in distal lower extremities.
- **Absent reflexes**, ↓ sensation, cranial nerve weakness (**facial palsy** in 50% cases).
- Autonomic function may be severely affected (e.g. cardiac irregularities, hypertension or hypotension).

Treatment

- **IV immunoglobulin (IVIg)**, **plasmapheresis**, physical therapy. Respiratory support until recovery.
- Almost all patients survive, **majority recover completely** after weeks to months.

D/D of Albuminocytologic dissociation

- Heavy metal intoxication (lead encephalopathy)
- Porphyria
- Botulism
- Spinal cord compression (Froin syndrome)
- Postdiphtheric paralysis

MULTIPLE SCLEROSIS

- **Autoimmune** mediated **demyelinating** disease, ↑ prevalence with ↑ **distance from equator** (↑ in **northern latitudes**).
- MC in **women in 20s and 30s**; MC in **whites**
- May present with **optic neuritis** (sudden loss of vision, **Marcus Gunn pupil**), **MLF syndrome (Internuclear ophthalmoplegia)**, hemiparesis, **Intentional tremor**, hemisensory symptoms, **scanning speech**, or bladder/bowel incontinence.
- O/E hyperreflexia, weakness, ataxia, **Lhermitte's sign** (Radiating/shooting pain up or down the neck on flexion/extension, **Heat sensitivity** (neurologic symptoms produced by an elevation of the body's core temperature – e.g. unilateral visual blurring may occur during a hot bath (**Uhthoff's symptom**)).
- **Acute MS (Marburg variant)**: Fulminant demyelination progressing to death within 1–2 years.
- CSF shows ↑ protein IgG (myelin basic protein, **oligoclonal bands**)
- Brain MRI with contrast: **Periventricular plaques** – **Dawson's fingers** (areas of oligodendrocyte loss and reactive gliosis with preservation of axons); **McDonald's MRI criteria** used
- **VEP** shows **delayed conduction**.

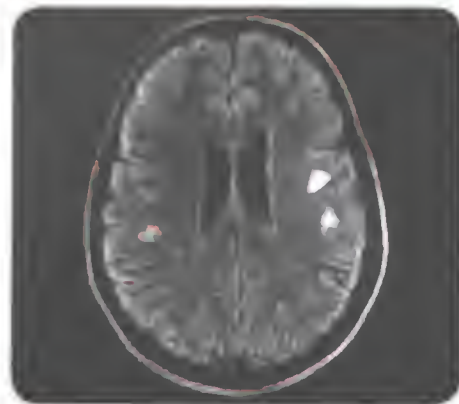


Fig. 21.33: Plaques

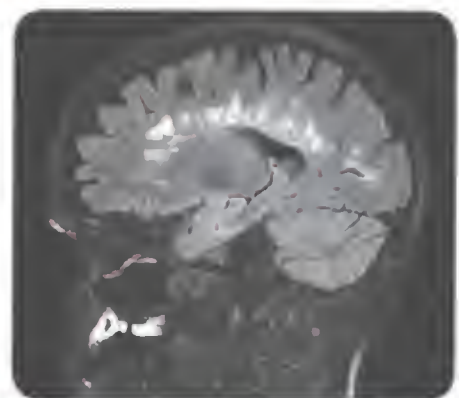


Fig. 21.34: Dawson's fingers

Treatment of MS

- ▶ Acute exacerbation with **IV methylprednisolone**
- ▶ Relapses and remissions with **b-interferon**
- ▶ **Glatiramer acetate**, a synthetic polymer of amino acids may reduce relapses
- ▶ **Baclofen** may be given for spasticity
- ▶ **Daflampridine**, a potassium channel blocker used for walking speed improvement in MS.
- ▶ **Fingolimod**, sphingosine 1-phosphate receptor modulator for relapsing forms of multiple sclerosis
- ▶ **Natalizumab** (alpha-4 integrin antagonist) and **teriflunomide** (pyrimidine synthesis inhibitor) and **alemtuzumab** (anti CD 52) for relapsing MS.
- ▶ **Ocrelizumab**—anti CD20 antibody for relapsing or primary progressive forms of MS.
- ▶ **Dimethyl fumarate** and **Alemtuzumab** are used for relapse prevention.

MYASTHENIA GRAVIS (MG)

- Bimodal distribution – women in 30–40s, men in 70–80s.
- Autoimmune disorder with **anti-acetylcholine receptor antibodies**.

- Fluctuating muscle weakness and **fatigability** it worsens towards end of the day.
- **Ocular MG**: Ptosis, diplopia; 50% go on to develop generalized myasthenia.
- **Generalized MG**: Bulbar (dysarthria, dysphagia, fatigable chewing), facial (expressionless), respiratory muscles.

Tests for Myasthenia Gravis

- ▶ **Tensilon (Edrophonium) test**: Tensilon is an acetylcholinesterase inhibitor that prolongs the presence of ACh at neuromuscular junction. A positive test results in an immediate ↑ in the strength of affected muscles.
- ▶ **Ice pack test**: Used in ptosis; ice pack over eyelids for 2 minutes improves ptosis.
- ▶ Immunologic assay for **MuSK antibodies**
- ▶ Single fiber EMGQ: Most sensitive diagnostic test for MG
- Treatment: **Pyridostigmine** (acetylcholinesterase inhibitor); surgery is **thymectomy**. (“EDrophonium for Diagnosis; pyRIDostigmine to get RID of symptoms”).

LAMBERT EATON MYASTHENIC SYNDROME (LEMS)

- **Lambert Eaton Myasthenic Syndrome (LEMS)** is caused by **autoantibodies directed against P/Q-type calcium channels at the motor nerve terminals (of the neuromuscular junction)**, which results in impaired release of ACh from nerve terminals.
- Proximal muscles of the lower limbs MC affected, CN involvement leads to ptosis and diplopia.
- LEMS is **a/w malignancy**, MC **small cell Ca of the lung**.
- Treatment: **Plasmapheresis**, **immunosuppression**, **3,4-Diaminopyridine (3,4-DAP)** acts by blocking potassium channels, which results in prolonged depolarization of the motor nerve terminals and thus enhances ACh release. **Pyridostigmine** prolongs the action of ACh, allowing repeated interactions with AChRs.

Differences between myasthenia gravis and LEMS are:

- ▶ Patients with **LEMS** have depressed/absent deep tendon reflexes (**BUT** paired in myasthenia), experience autonomic changes such as dry mouth and impotence
- ▶ On repetitive nerve stimulation, **have incremental** rather than decremental responses.

BELL'S PALSY

- The MC form of facial paralysis is **idiopathic**, i.e., **Bell's palsy**. (**infranuclear or LMN type**)
- Bell's palsy maybe a/w presence of **HSV type 1 DNA**; recipients of **inactivated intranasal influenza vaccine**.

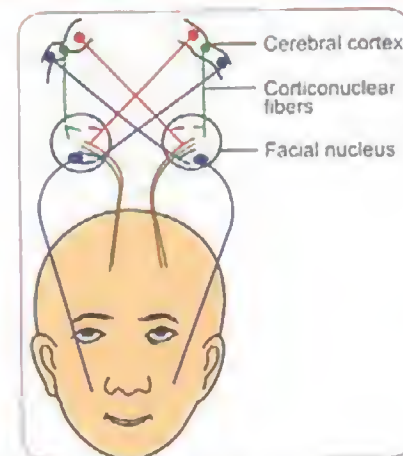


Fig. 21.35: Corticonuclear connections of facial nucleus (Note the bilateral control of upper face and contralateral control of lower face)

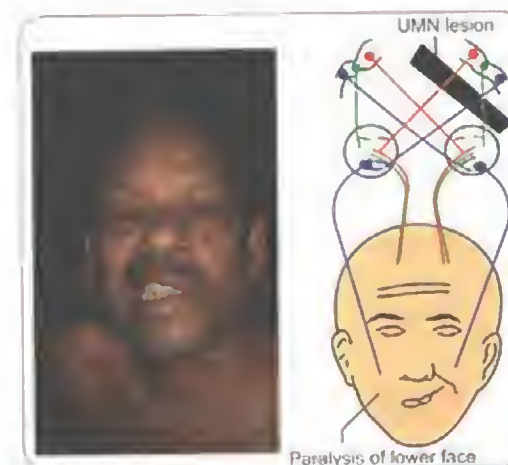


Fig. 21.36: UMN facial palsy on right side (In the diagram) and features of UMN facial palsy in a patient on left side



Fig. 21.37: Infranuclear lesion of right facial nerve (in the diagram) and left LMN facial palsy in the patient

- **Clinically**: Loss of horizontal wrinkles on forehead; inability to close the eye; epiphora; loss of corneal reflex; absent nasolabial fold; inability to show the teeth; while smiling affected side remains motionless and mouth is drawn to normal side.
- Abrupt onset; maximal weakness being attained by 48 h as a general rule.
- Pain behind the ear may precede the paralysis for a day or two.
- Taste sensation may be lost unilaterally, and hyperacusis may be present.
- In some cases there is mild CSF lymphocytosis.
- **MRI** may reveal swelling and uniform enhancement of the geniculate ganglion and facial nerve and, in some cases, entrapment of the swollen nerve in the temporal bone.
- Approximately **80% of patients recover within a few weeks or months**.
- **Electromyography** for some prognostic value (evidence of denervation after 10 days indicates there has been axonal degeneration, that there will be a long delay (3 months as a rule) before regeneration occurs, and that it may be incomplete).
- The presence of **incomplete paralysis in the first week** is the most favorable prognostic sign.

D/D of facial palsy

- ▶ Ramsay Hunt syndrome
- ▶ Leprosy
- ▶ Diabetes mellitus
- ▶ Connective tissue diseases including Sjögren's syndrome
- ▶ Amyloidosis.
- ▶ Acoustic neuroma
- ▶ Lyme disease (uni or bilateral)
- ▶ Sarcoidosis and Guillain-Barre syndrome (bilateral)
- ▶ **Melkersson-Rosenthal syndrome** consists of recurrent facial paralysis; recurrent—and eventually permanent—facial (particularly labial) edema; and, less constantly, plication of the tongue.

Treatment

- **Glucocorticoids**. (prednisone) **shortens the recovery period** and modestly improves the functional outcome; physiotherapy; NO added benefit of acyclovir.

TYPES OF SEIZURES

Type	Clinical	Involvement/EEG
Focal		
▪ Simple partial	Focal sensory (e.g., paresthesias, hallucinations -“something crawling inside my head”) or motor (e.g., repetitive or purposeless movement) activity, no loss of consciousness; focal neurologic deficits lasting several minutes to hours after seizure (i.e., Todd paralysis); “ Jacksonian march ” (abnormal motor movements may begin in a very restricted region such as the fingers and gradually progress (over seconds to minutes) to include a larger portion of the extremity)	Focal cortical region of brain
▪ Complex partial	Hallucinations (e.g., auditory, visual, olfactory), automatisms (i.e., repeated coordinated movement), <i>déjà vu</i> , impaired consciousness, postictal confusion	Focal abnormalities in temporal lobe
Generalized		
▪ Generalised convulsive	Sustained contraction of extremities and back (tonic); repetitive muscle contraction and relaxation (clonic); brief contraction period followed by repetitive contraction-relaxation (tonic-clonic); brief repetitive contractions (myoclonic); loss of tone (atonic); loss of consciousness, incontinence, significant postictal confusion	Bilateral cerebral cortex involved; generalized EEG abnormalities
▪ Absence seizures (Petit Mal)	Absence seizures usually begin in <i>childhood (ages 4–8) or early adolescence</i> Accounts for 15-20% of childhood epilepsy Clinically: Brief attacks of transient loss of consciousness without the patient collapsing to the ground. can occur hundreds of times per day ; “ daydreaming ” and a decline in school performance recognized by a teacher; NOT associated with postictal confusion.	EEG hallmark is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background.

First Aid for Epilepsy/Seizures

DO	DO NOT
<ul style="list-style-type: none">Protect the person from injury - (remove harmful objects from nearby)Cushion their headLook for an epilepsy identity card or identity bracelet/chainAid breathing by gently placing them in the recovery position once the seizure has finished (right/left lateral position)Stay with the person until recovery is completeBe calmly reassuring	<ul style="list-style-type: none">Restrain the person’s movementsPut anything in the person’s mouthTry to move them unless they are in dangerGive them anything to eat or drink until they are fully recoveredAttempt to bring them round

Features that Distinguish Seizure (Generalized Tonic-Clonic) from Syncope

Characteristics	Seizure	Syncope
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, Orthostasis hypotension, cardiac etiology
Premonitory symptoms	None or aura (ex: odd smells)	Tiredness, nausea, sweating, tunnelling of vision
Posture at onset	Variable	Usually erect

Contd...

Characteristics	Seizure	Syncope
Transition to unconsciousness	Often immediate	Gradual over seconds
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30-60s	Never more than 15 seconds
Facial appearance during event	Cyanosis, frothing at mouth	Pallor

Contd...

Contd.

Contd...

Characteristics	Seizure	Syncope
Disorientation and sleepiness after event	Many minutes to hours	< 5 minutes
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

Status Epilepticus (SE)

- This refers to **continuous seizures** or **repetitive, discrete seizures** with impaired consciousness in the interictal period.
- The duration of seizure activity sufficient to meet the definition of status epilepticus has traditionally been specified as **15–30 min**.

• Practical definition is to consider status epilepticus as any situation in which the duration of seizures prompts the acute use of anticonvulsant therapy. For GCSE (generalise convulsive status epilepticus), this is typically when seizures last **beyond 5 min**.

- Treatment:**
 - **Impending and early SE** (5–30 minutes): start **IV BZD** (lorazepam, clonazepam or midazolam) + **IV anti-epileptic** drug (Phenytoin, valproate or levatricetam)
 - **Established and refractory SE** (30 mins to 48 hours): **IV midazolam** or **IV propofol**
 - **Late refractory SE** (> 48h): **Pentobarbital** or **thiopentone sodium**.

PHAKOMATOSES (NEUROCUTANEOUS DISEASES)

Because the **nervous system develops from the epithelial layer of the embryo**, a number of congenital diseases include both **neurologic and cutaneous manifestations**.

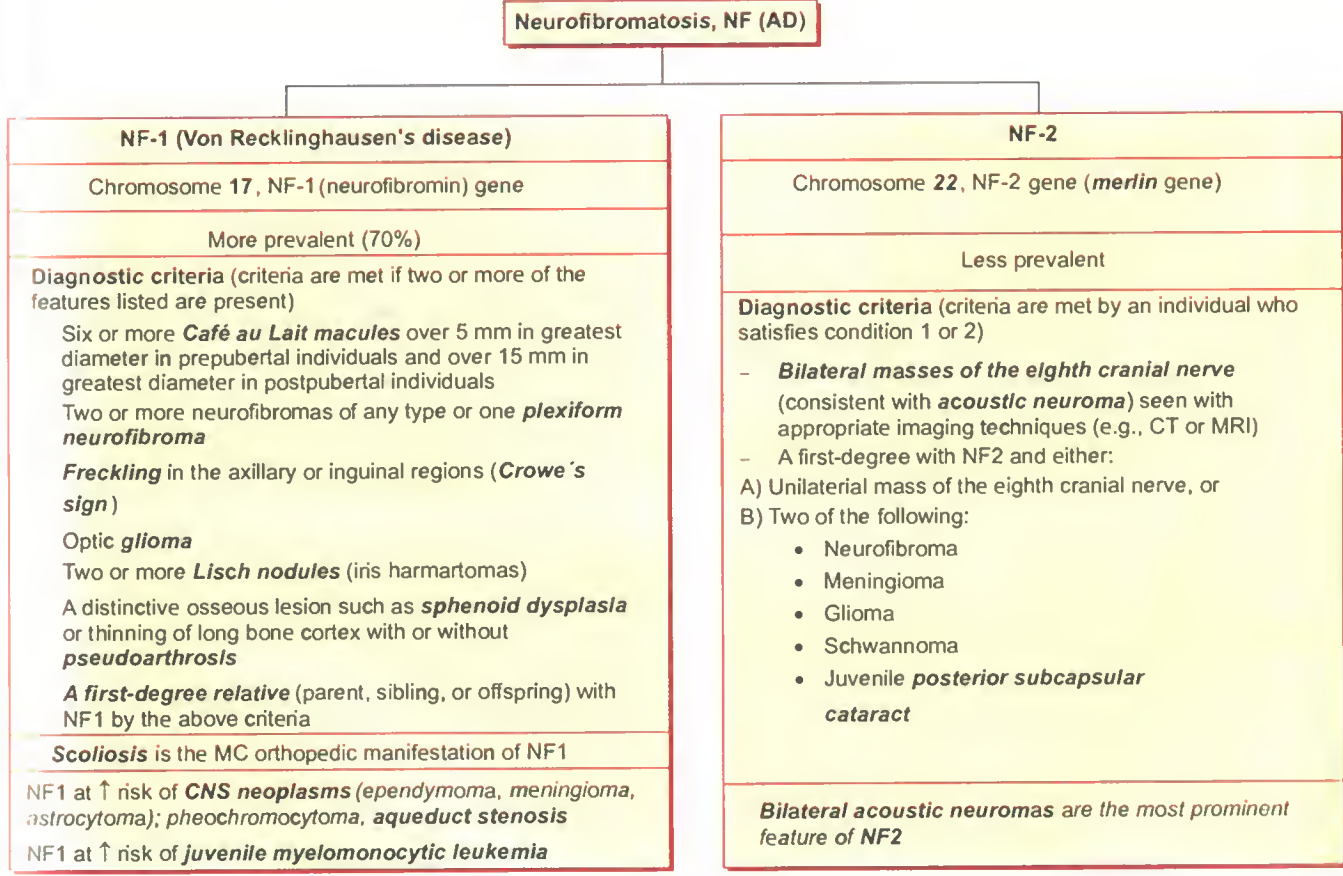




Fig. 21.38: Neurofibromatosis



Fig. 21.39: Plexiform neurofibromatosis

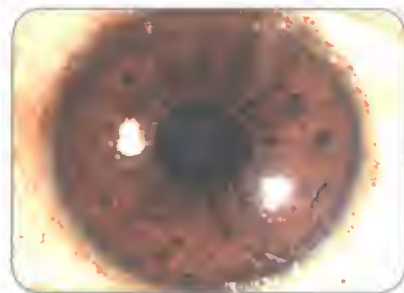


Fig. 21.40: Lisch nodules—LE—neurofibromatosis—same patient



Fig. 21.41: Cafe

Tuberous Sclerosis (Bourneville's disease)

- Triad of Tuberous sclerosis = = **EPI**lepsy (seizures), **LOw I** (mental retardation) and Adenoma sebaceum = **Vogt's triad** = also known as "**EPILOIA**"
- Seizures detected in infancy as **myoclonic jerks**; important cause of **West syndrome**; treated with **viagabatrln**
- **AD** inheritance; mutations in **TSC1 gene (hamartin)** on chromosome 9 or the **TSC2 (tuberin gene)** on chromosome 16 resulting in constitutive expression of **mTOR (mammalian target of rapamycin)** and impaired tumor suppression in multiple tissues
- CNS lesions: **subependymal nodules (a/w calcification)**, cortical **tubers**, **white matter** abnormalities and **subependymal giant-cell astrocytomas (SEGA)**; most effective Rx of SEGA is mTOR inhibitors - sirolimus and everolimus.

Features of Tuberous Sclerosis**Skin findings**

- **Adenoma sebaceum**, at 5-10 years of age, reddened nodules on the face (cheeks, nasolabial folds, sides of the nose, and chin) and sometimes on the forehead and neck.
- **Koenen's subungual fibromas**
- **Shagreen patches** (leathery plaques of subepidermal fibrosis, situated usually on the trunk)
- **Ash leaf-shaped hypopigmented spots** - **earliest skin sign**

Other abnormalities

- Retinal astrocytoma (mulberry like)
- Benign cardiac rhabdomyomas
- Benign tumors in the viscera
- Dental pits
- Lung and Bone cysts
- Periosteal thickening
- Pulmonary fibrosis

Renal lesions

- Kidneys affected in 80% of patients.
- Renal cysts
- **Renal angiomyolipomas**
- **Renal cell carcinoma**



Fig. 21.42: Father (adenoma sebaceum) and son (ash leaf macules) affected with tuberous sclerosis



Fig. 21.43: Tuberous sclerosis—mulberry-like astrocytoma



Fig. 21.44: Koenen tumor

- **Erythropoietin** produced by hemangioblastomas may result in **polycythemia**.
- **Autosomal dominant**, chromosome 3p.



Fig. 21.45: Angiomatosis retinae—von Hippel-Lindau disease

Sturge-Weber Syndrome

- Unilateral cutaneous angioma and **portwine stain** involving upper face; **leptomenigeal angiomatosis**; **choroidal angioma**; **unilateral glaucoma** on the same side and **focal seizures**.
- Skull X-rays may show '**tram track**' intracranial calcification.
- A/w **GNAQ mutation** in 90% cases.

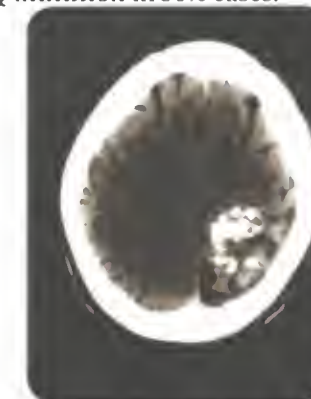


Fig. 21.46: CT scan of the patient shows gyral calcification in the same patient. Patient had epilepsy for more than 10 years

Von Hippel-Lindau syndrome (AD)

Characteristic tumors/cysts
Hemangioblastomas of

- Cerebellum
- Retina
- Spinal cord
- Brainstem (medulla)

Other tumors/cysts

- Renal cell carcinoma
- Pheochromocytoma
- Renal adenoma/cysts
- Pancreatic endocrine tumours
- Adrenal carcinoma
- Benign cysts in skin, liver, epididymis

FEW OTHER IMPORTANT TOPICS**Progressive Multifocal Leukoencephalopathy (PML)**

- **PML** is a **progressive demyelinating disorder** involving the brain BUT **sparing the optic nerves and spinal cord**.
- Typically a/w immunosuppression and **HIV** infection; caused by JC virus.
- **Brain biopsy is diagnostic** and shows demyelination, enlarged astrocytes and oligodendrocytes.

- Clinically: *visual symptoms (homonymous hemianopia); dementia; ataxia, seizures.*
- Treatment: with anti-retroviral therapy.

HSV Encephalitis

- The clinical hallmark of HSV encephalitis has been the acute onset of fever and focal neurologic symptoms and signs, especially in the **temporal lobe**.
- In HSV encephalitis - **Elevated CSF protein** levels, leukocytosis (predominantly **lymphocytes**), and **RBC counts** due to **hemorrhagic necrosis** are common.
- While **brain biopsy has been the gold standard** for defining HSV encephalitis, a highly sensitive and specific **PCR for detection of HSV DNA in CSF** has largely replaced biopsy for defining CNS infection.
- Due to **high mortality rate**; start **IV Acyclovir for 10 days** or more.

Complex Regional Pain Syndrome

CRPS type I (Reflex sympathetic dystrophy)	CRPS type II (Causalgia)
<ul style="list-style-type: none">• A regional pain syndrome that usually develops after tissue trauma. (ex: myocardial infarction, minor shoulder or limb injury, and stroke).• Allodynia (the perception of a nonpainful stimulus as painful), hyperpathia (an exaggerated pain response to a painful stimulus), and spontaneous pain occur.• Symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve.	<ul style="list-style-type: none">• A regional pain syndrome that develops after injury to a peripheral nerve, usually a major nerve trunk.• Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

Chronic and Persistent CNS Infections

Disease	Agent
Progressive multifocal leukoencephalopathy (PML)	JC virus
Subacute sclerosing panencephalitis (SSPE)	Measles virus
Tropical spastic paraparesis	HTLV 1

Prion Diseases

- **PRION** = **Proteinaceous infectious protein particle** that **lacks nucleic acid** (NO DNA or RNA). Prions are composed largely, if not entirely, of **PrPSc molecules**.

Human prion diseases	Animal prion diseases
<ul style="list-style-type: none">• Creutzfeldt Jakob disease (MC)• Gerstmann Straussler Scheinker disease• Fatal Familial insomnia• Kuru	<ul style="list-style-type: none">• Scrapie• Bovine spongiform encephalopathy, and• Chronic wasting disease

Signs of Basal Skull Fracture

- **Battle's sign**: Postauricular ecchymoses, (over mastoid process).
- **Panda/Raccoon eyes**: Periorbital ecchymoses
- **Hemotympanum** (blood behind the eardrum) Fracture of petrous ridge
- **CSF otorrhea or rhinorrhea** (leakage of CSF, which is clear in appearance, from the ears or nose).

SPINAL CORD DISEASE

Syringomyelia
<ul style="list-style-type: none">• Enlargement of central canal (syrinx) of spinal cord. Crossing fibres of spinothalamic tract are damaged.• Bilateral loss of pain and temperature sensation in upper extremities with preservation of light touch sensation (Dissociated Sensory Loss)• May be present in patients with Arnold-Chiari malformation• MC at C8-T1
Brown Sequard syndrome
<ul style="list-style-type: none">• Hemisection of spinal cord. Findings are:• Ipsilateral UMN signs (corticospinal tract) below the lesion• Ipsilateral loss of tactile, vibration, proprioception sense (dorsal column) below lesion• Ipsilateral loss of all sensation and presence of LMN signs (e.g., flaccid paralysis) at level of lesion• Contralateral pain and temperature loss (spinothalamic tract) below lesion• If lesion occurs above T1, presents with Horner's syndrome
Tabes dorsalis
<ul style="list-style-type: none">• Degeneration of dorsal columns and dorsal roots due to tertiary syphilis resulting in impaired proprioception and locomotor ataxia.• A/w Charcot's joints, shooting (lightning) pain,• Argyll Robertson Pupil (Accommodation Reflex Present, light reflex absent)• Absent deep tendon reflexes

EXTRA EDGE

- **Priapism** is a strong predictor of **severe spinal cord injury** even in **intubated patients**.

Clinical Features of Cerebellar Disease

- **Truncal Ataxia** (of gait): unsteadiness with a wide base, body sway, and an inability to walk on tandem (heel to toe); (if ataxia worsens on eye closure, lesion is in the dorsal columns, not cerebellum).
- **Dysarthria (dyssynergia)** refers to a decomposition of movement instead of a smooth, continuous movement; it is associated with a tendency to miss a target and worsens when approaching the target.
- **Dysmetria** (the misjudging of distance), with its characteristic overshooting and undershooting of a target (**past-pointing**).
- **Intentional tremor**
- **Dysidiadochokinesia** (*inability to perform rapidly coordinated movements such as pronation and supination of hands*)
- **Nystagmus**
- **Scanning speech**
- **Hypotonia**
- **Decomposition of movements**.

Other brain hemorrhages

Location	Clinical features
Putaminal hemorrhage	<ul style="list-style-type: none">• MC site for hypertensive hemorrhage (50-60% cases) (Harrison's, 17th/2532)• Contralateral hemiparesis is sentinel sign since adjacent internal capsule is damaged
Thalamic hemorrhage	<ul style="list-style-type: none">• Contralateral hemiparesis• Prominent sensory deficit involving all modalities• Ocular disturbances
Pontine hemorrhage	<ul style="list-style-type: none">• Deep coma with quadriplegia usually occurs over a few minutes• Prominent decerebrate rigidity and• "pin-point" (1 mm) pupils• Hyperpnea, severe hypertension, and hyperhidrosis are common.• Death often occurs within a few hours, but small• Hemorrhages are compatible with survival.
Cerebellar hemorrhage	<ul style="list-style-type: none">• Rarely• Develop over several hours• Occipital headache• Repeated vomiting• Ataxia, paralysis of conjugate lateral gaze towards the side of hemorrhage

PUPILS AND PHYSIOLOGIC ASPECTS OF NEURO-OPHTHALMOLOGY

Neurons of Visual Pathway

I order neuron	II order neuron	III order neuron	Mnemonic
Bipolar cell in the retina	Ganglion cell of the retina	Lateral geniculate body cells	"I, II, III = "BuGLE"

Pupillary Reflexes

Reflex	Pathway
<ul style="list-style-type: none">• Light reflex: If light enters the eye, the pupil constricts (direct light reflex); and there is an equal constriction of pupil of the other eye (consensual light reflex)	Rods and cones → optic nerve → optic chiasma (partially decussate) → optic tract → pretectal nucleus (instead of running to lateral geniculate body) → partial decussation in midbrain → Edinger-Westphal nucleus on each side → III CN → inferior division → branch to inferior oblique → short root of ciliary ganglion → ciliary ganglion → short ciliary nerves → sphincter pupillae
<ul style="list-style-type: none">• Near reflex: A constriction of pupil occurs on looking at near object, a reflex largely determined by the reaction to convergence.	Medial rectus muscle → via third (oculomotor) nerve → mesencephalic nucleus of V CN → presumptive centre for convergence at pons → Edinger-Westphal nucleus → along the third nerve → accessory ciliary ganglion → sphincter pupillae
<ul style="list-style-type: none">• Psychosensory reflex:	a dilatation of pupil occurs on psychic or sensory stimuli

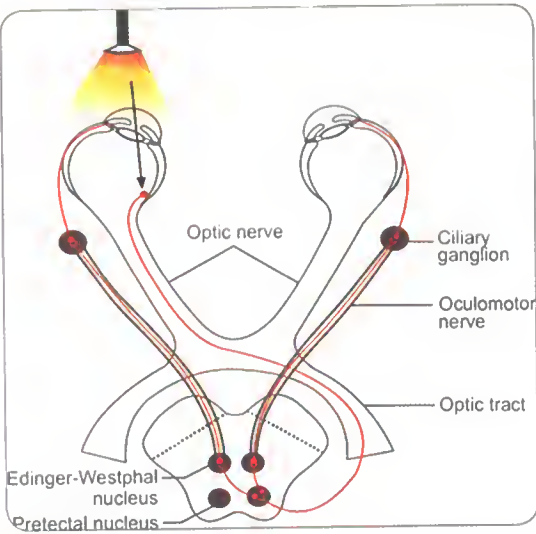


Fig. 21.47: Pathways of pupillary light reflexes (direct and consensual)

Pupil and Pupillary Abnormalities

- **Sphincter Pupillae** – ParaSympathetic, III CN (Oculomotor .N).
- **Dilator pupillae** – Sympathetic (cervical sympathetic nerve).
- **Anisocoria** – **Inequality** in pupil size
- **Aniseikonia** – Different **size of images** (magnifications) in both eyes
- **Hippus** – An alternate rhythmic contraction and dilation of pupil.
 - Seen in **normals, multiple sclerosis, aconite poisoning.**
- **Relative Afferent Pupillary Defect (RAPD) or Marcus-Gunn pupil**
 - It occurs in defect of the visual pathway **anterior to the chiasma** – **most characteristic of optic N lesions** – Best seen in **unilateral optic neuritis**
 - Can be detected by the “**Swinging flashlight test**” – Normally if a penlight is alternately directed to each eye, the pupils constrict and do not vary as the light alternates between the eyes.
 - In RAPD, both pupils **dilate** when the light is moved from the unaffected to the affected eye, but they constrict when the light is moved to the normal eye.
- **Argyll-Robertson Pupil**
 - Also called “**prostitute’s pupil** (only accommodates, doesn’t react!)”
 - Accommodation Reflex Present; Light Reflex absent – ‘Light Near dissociation’.

Contd...

- Pupils are miotic, unequal, irregular, eccentric; atrophic depigmented patches on iris seen.
- Pupils fail to dilate with mydriatic, but constrict further with eserine.
- Presence of good vision in both eyes.
- Causes: **tabes dorsalis; diabetes mellitus;** multiple sclerosis.
- Site of lesion: Internuncial neurones between pretectal nucleus and Edinger-Westphal nucleus at the level of pretectum
- **Adie’s Pupil (Tonic Pupil)**
 - **Unilateral dilated** pupil; Occurs in healthy young women (30-40 years); also seen in Shy-Drager syndrome, segmental hypohidrosis, diabetes and amyloidosis.
 - With 0.125% pilocarpine, denervation hypersensitivity produces pupillary constriction in a tonic pupil, whereas the normal pupil shows no response.
 - The Adie’s pupil dilates with atropine but the Argyll Robertson pupil does not.
 - Adie’s pupil constricts to near stimulus BUT reacts poorly to light.
 - **Holmes Adie’s pupil** – Adie’s pupil + with **weak or absent tendon reflexes** in the in the lower extremities (absent knee jerks or ankle jerks).
- **Wernicke’s hemianopic pupil**
 - Seen in **optic tract lesions.** The pupillary light reflex will be normal when the unaffected hemietina is stimulated and absent when the involved hemiretina is stimulated (i.e. light is shone from the hemianopic side).

Contd...

Neurological Visual Field Defects

Site/Cause of lesion	Defect	Causes
• Anterior ischemic optic neuropathy	Altitudinal field defect (usually inferior)	Giant cell arteritis (see below), Diabetes, hypertension,
• Old / Toxic optic neuritis	Centrocecal field defect	Tobacco, alcohol, ethambutol
• Optic N.	Complete field defect	Avulsion, atrophy
• Posterior part of optic N. and anterior optic chiasma	Junctional scotoma (ipsilateral central scotoma with contralateral upper temporal defect)	Tuberculum sellae meningioma – causes damage to anterior knee of von Willebrand
• Optic chiasma	Bitemporal hemianopia	Pituitary adenoma (superotemporal field affected first) (“like beating of a drum from up to down!!”) Craniopharyngioma (inferotemporal field affected first)
• Lateral chiasmal lesion	Binasal hemianopia	Distension of third ventricle (rare)
• Optic tract	Incongruous homonymous hemianopia	Aneurysm of superior cerebellar or posterior cerebral A.,

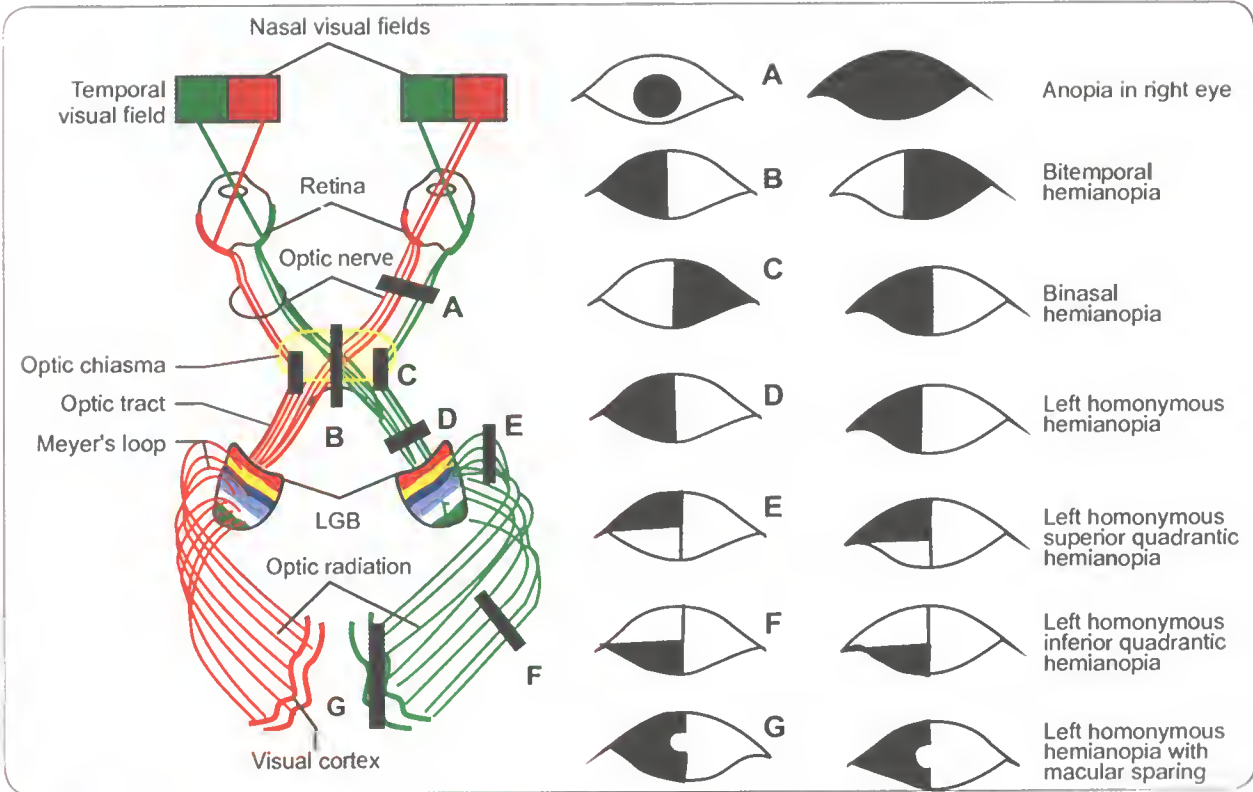
Contd...

Contd ..

Site/Cause of lesion	Defect	Causes
• Lateral geniculate body (LGB) lesions	“Wedge” shaped homonymous hemianopia - sectoranopia or “keyhole” defect	
• Temporal optic radiation (Meyer’s loop)	Superior quadrantic hemianopia (“Pie in the sky”)	Temporal lobe lesions
• Parietal optic radiation	Inferior quadrantic hemianopia (“Pie on floor”)	Parietal lobe lesions
• Anterior occipital cortex	Congruous homonymous hemianopia with macular sparing ; bilateral homonymous hemianopia with macular sparing - gives rise to residual “keyhole” visual field	Occlusion of posterior cerebral A.
• Tip of occipital cortex	Congruous homonymous macular defect	Head injury, Gunshot injury

EXTRA EDGE

- Pupillary reaction is **NORMAL** in lesions beyond optic tract (i.e. LGB, optic radiation, occipital cortex) as fibres of light reflex leave optic tracts to synapse in the superior colliculi.
- Descending optic atrophy does **NOT** occur in lesions beyond LGB (i.e. optic radiation and occipital cortex) as the first order neurons synapse in LGB.
- The **more posterior** the lesion in the visual pathway, the **more congruous** is the field defect.



Figs. 21.48A to G: Visual field defects due to lesions of visual pathway at various sites

Horner's Syndrome

Clinical features	Causes
Horner syndrome (oculosympathetic paralysis) consists of: <ul style="list-style-type: none">▪ Miosis (due to unopposed action of sphincter pupillae - parasympathetic)▪ Ptoxis and Enophthalmos (due to loss of tone of Muller's muscle)▪ Anhidrosis (unilateral) – ONLY if lesion is below the superior cervical ganglion▪ Loss of ciliospinal reflex▪ In congenital Horner's, iris is hypochromic	<ul style="list-style-type: none">▪ Central (first-order neuron):<ul style="list-style-type: none">– Brainstem disease (tumor, vascular, demyelination)– Syringomyelia– Lateral medullary syndrome (Wallenberg)– Spinal cord tumor– Diabetic autonomic neuropathy▪ Pre-ganglionic (second-order neuron):<ul style="list-style-type: none">– Pancoast tumor (apical lung tumor)– Carotid and aortic aneurysm and dissection– Neck lesions (glands, trauma, postsurgical)▪ Postganglionic (third-order neuron):<ul style="list-style-type: none">– Cluster headache– Internal carotid artery dissection– Nasopharyngeal tumor– Otitis media– Cavernous sinus mass

- **Cocaine confirms** diagnosis of Horner syndrome
- **Hydroxyamphetamine** (Paredrine) **differentiates** between a **preganglionic** and **postganglionic** lesions.

Retinal Ganglion Cell (RGC) Pathways

	M (Magnocellular cells)	P (Parvocellular cells)	K (Konio cells)
Subset of RGC	Parasol	Midget	Bistratified (blue-on)
Percentage of RGC	10%	80%	9%
Projection to Lateral geniculate body	Magnocellular layers (layers 1, 2)	Parvocellular layers (layers 3, 4, 5, 6)	Interlaminar
Most sensitive to	Motion perception, contrast sensitivity, broadband light perception, stereo vision	Central visual acuity, form sense, Red green opponency	Blue yellow opponency

- **Blobs:**
 - These are clusters of cells arranged in mosaic *layers 2, 3 of visual cortex—concerned with color vision*
- **Visual cycle (Rhodopsin cycle):**
 - Visual phototransduction is a process by which light signals are converted into electrical signals in rods and cones and ganglion cells of retina.
 - **Rhodopsin** is the visual pigment in *outer segments of rods responsible for scotopic vision (dark/night vision)*.
 - Rhodopsin activates transducin upon absorption of light.

OPTIC NEURITIS

Optic neuritis is an acute or subacute inflammatory or demyelinating process affecting the optic nerve.

- Etiology
 - **Demyelinating:** **MC is multiple sclerosis**, neuromyelitis optica (Devic's disease), Schilder's disease.
 - **Parainfectious:** May follow a *viral infection* (measles, mumps, chicken pox, whooping cough, glandular fever) or immunization.
 - **Infectious:** May be sinus-related or associated with cat scratch fever, syphilis, Lyme disease, and cryptococcal meningitis in AIDS patients.
- **Clinical features:**
 - **Sudden diminution of vision** (maybe reduced to counting fingers or PL only).
 - Deep orbital or **retroocular pain aggravated by eye movement** or digital pressure on the globe (due to inflammation of at the site of insertion of *superior rectus tendon*)
 - **Color vision abnormality (red green deficiency)**
 - Depth perception, particularly for moving objects may be impaired (**Pulfrich's phenomenon**)
 - **Relative Afferent Pupillary Defect (RAPD or Marcus Gunn pupil)**
 - **Fundus:**
 - **Papillitis:** **MC type of optic neuritis in children**, usually *postviral*. Affecting part of the optic nerve ophthalmoscopically visible at the disc and therefore showing obvious signs – **optic disc swelling/edema, peripapillary flame shaped hemorrhages**.
 - **Neuroretinitis:** Papillitis + **macular involvement (macular star** composed of hard exudates);

least common type of optic neuritis; due to viral infections, cat scratch fever, syphilis, Lyme disease.

- **Retrobulbar neuritis: MC type of optic neuritis in adults;** usually due to **multiple sclerosis**. Affects the proximal optic nerve so that NO ophthalmoscopic changes are seen (**optic disc appears normal**) – so the diagnosis has to be made mainly clinically {described as “Patient can't see anything, Doctor can't see anything (abnormal)!!”}
- **Treatment** consist of **pulsed IV methylprednisolone** followed by oral prednisolone. ONTT (Optic neuritis Treatment Trial) showed that IVMP reduces initial progression to CDMS (Clinically Definite Multiple Sclerosis) for 3 years. **NEVER** use oral prednisolone as initial therapy since it increases risk of recurrence.

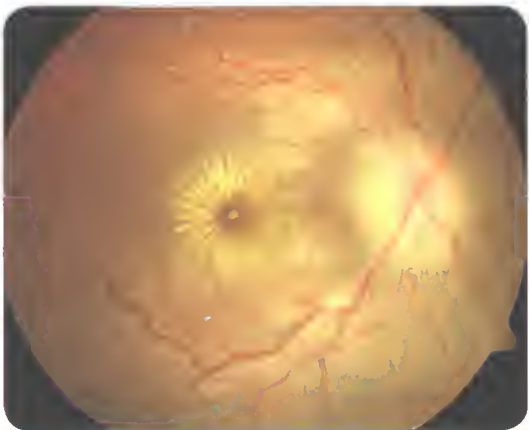


Fig. 21.49: Neuroretinitis with macular star

PAPILLOEDEMA

- Papilloedema is the **bilateral, passive swelling of the optic nerve head** secondary to **raised intracranial pressure (> 20 cm H₂O)**. All patients with papilloedema should be suspected of having an **intracranial mass** unless proved otherwise.
- However “**disc edema**” may be **unilateral/bilateral** and include all causes of active or passive edematous swelling of the optic disc and may be due to **local inflammation, vascular disorders or compressive lesions** in the orbit.
- Patients who have had papilloedema earlier (or optic atrophy earlier) may develop substantial increase in intracranial pressure but fail to re-develop papilloedema because of **glial scarring of the optic nerve head**.

- **Pathogenesis:** **intrinsic swelling of ganglion cell axons due to stasis of orthograde axoplasmic flow in prelaminar optic nerve head.**

Etiology:

- **Intracranial space occupying Lesions (ICSOLs)** including tumors, abscesses, aneurysm and intracranial hemorrhage—ICSOLs in any position **except medulla oblongata** may produce papilloedema. Papilloedema is more frequently a/w **tumors arising in the posterior fossa**, which obstruct aqueduct of sylvius and least with pituitary tumours. Thus ICSOLs of posterior fossa (cerebellum, midbrain, parieto-occipital region) produce papilloedema **more rapidly** than those in the cerebrum.
- **Benign intracranial hypertension (pseudotumor cerebri)**—seen in **obese young women** as **chronic headache** with **bilateral papilloedema** with no localizing neurologic signs. Mainly occurs as a side effect of certain drugs like—**Hypervitaminosis A, Oral contraceptives, Tetracyclines, Nalidixic acid, Amiodarone, Glucocorticoids (“HOT-NAG”)**
- **Malignant hypertension.**
- **Congenital stenosis of ventricular system:** aqueductal stenosis, craniosynostosis.
- **Obstruction of CSF absorption** via arachnoid villi, previously damaged by meningitis, subarachnoid hemorrhage or cerebral trauma.
- Hypersecretion of CSF by choroids plexus tumor (very rare).
- Diffuse cerebral edema from blunt head trauma.

Clinical features of papilledema:

- **Headache, sudden nausea and projectile vomiting, focal neurological deficits** with changes in level of consciousness.
- **Visual acuity and pupillary reactions remain fairly normal** until the late stages of the disease. **Amaurosis fugax**—a transient blackout of vision for a few seconds may be present in some patients. VF are usually normal. **Horizontal diplopia**, which is caused either by involvement of third nerve or stretching of the sixth nerve over the petrous tip.

Signs:

- **Early papilloedema: Blurred disc margins (earliest sign)—nasal margins involved first; optic disc hyperemia; loss of previous spontaneous venous pulsation (SVP).** If SVP is well preserved, diagnosis of papilloedema is unlikely (NOTE: in 20% of normal's, SVP may be absent)

- **Established papilloedema:** Severe optic disc hyperemia, moderate elevation (**1 mm elevation = + 3D**), indistinct disc margins, venous engorgement, peripapillary flame-shaped hemorrhages, cotton-wool spots. Hard exudates around the macula in form of a “macular star”. **Blind spot is enlarged.**
- **Longstanding/Chronic papilloedema:** VA is variable and VF show constriction. Optic disc markedly elevated with a ‘**champagne cork**’ appearance. Cotton wool spots and haemorrhages are absent (have subsided). Optociliary shunts, drusen like crystalline deposits on the disc surface and **Paton’s lines** (concentric retinal folds around disc) may be present.
- **Atrophic papilloedema:** VA is **severely impaired**. Optic disc is **white, slightly elevated**, crossing blood vessels are few and margins are indistinct—**secondary optic atrophy**—MC seen in patients with a history of treated cerebral tumors or benign intracranial hypertension.

Treatment:

- Treat the cause. Surgical decompression of optic nerve may be indicated to preserve vision.



Fig. 21.50: Established papilledema—flame shaped hemorrhage—LE

Differences between Papilledema and Papillitis (Optic Neuritis)

	Papilledema	Papillitis (Optic neuritis)
History	Headache and vomiting, initially NO visual symptom	Sudden loss of vision, h/o fever or URTI

Contd...

	Papilledema	Papillitis (Optic neuritis)
Laterality	Usually Bilateral	Usually unilateral
Visual acuity	Remains normal until late stage	Severely reduced (6/60 or less)
Pain or tenderness of the eyeball	Absent	May be present
Pupil	Normally reacting	Relative Afferent Pupillary Defect (RAPD) or Marcus Gunn Pupil
Disc swelling	More than +3D elevation in established case	Usually +2D to +3D elevation
Hemorrhage and exudates	More in established case	Relatively less
Visual fields	Enlargement of blind spot and later constriction of peripheral fields	Central or centrocecal scotoma
CT scan or MRI	Intra cranial space occupying lesion (ICSOL) can be detected	Demyelinating disorder can be seen
Recovery of vision	Usually not complete after treatment	Usually complete with adequate and prompt treatment

OPTIC ATROPHY

- **Definition:** Optic atrophy is a **degeneration of the optic nerve**, which occurs as an end result of any pathological process that damages axons in the **anterior visual system, i.e. from retinal ganglion cells to the lateral geniculate body.**

Etiological Classification

Primary Optic Atrophy

- It refers to simple degeneration of nerve fibres **without antecedent swelling of optic nerve head**. It is caused by lesions affecting the visual pathways from the retrolaminar portion of the optic nerve to the lateral geniculate body. Lesions affecting the optic nerve (anterior to the chiasm) will result in unilateral optic atrophy whereas those involving the chiasm and optic tract will cause bilateral optic atrophy. **Foster-Kennedy syndrome** is characterized by **optic atrophy in one eye and disc edema in the other.**

Contd...

- **Tabes dorsalis**
- Following **optic/retrobulbar neuritis**
- Compressive by tumors and aneurysms.
- Hereditary optic neuropathies (**Leber’s optic atrophy**).
- Toxic (methanol) and nutritional optic neuropathies.
- Trauma
- **Wolfram syndrome (DIDMOADQ):** Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness).
- **Disc appearance:** **Chalky white, flat disc with clearly delineated margins;** reduction in number of blood vessels crossing the disc; attenuation of peripapillary blood vessels and thinning of retinal nerve fibre layer.

Secondary optic atrophy	Consecutive optic atrophy	Glaucomatous optic atrophy
<ul style="list-style-type: none">• It is preceded by swelling of the optic nerve head.<ul style="list-style-type: none">– Papilloedema– AION– Papillitis• Disc appearance: white or dirty grey, slightly raised disc with poorly delineated margins; reduction in number of blood vessels crossing the disc (Kestenbaum’s sign).	<ul style="list-style-type: none">• It occurs following destruction of ganglion cells secondary to degenerative or inflammatory lesions of the choroids and/or retina.<ul style="list-style-type: none">– Retinitis pigmentosa– CRAO– Pathological myopia– Extensive retin-choroiditis– Retinal necrosis– Excessive retinal photocoagulation– Old vasculitis	<ul style="list-style-type: none">• It occurs following raised IOP.

Anatomical Classification

- **Ascending optic atrophy:** Here the lesion is in the retina and an ascending optic atrophy occurs which terminates in the lateral geniculate body.
- **Descending optic atrophy:** This follows disease involving the optic nerve fibres anterior to the lateral geniculate body, and terminates at the optic disc e.g. chiasmal compression, retrobulbar neuritis.
- **“BOW-TIE” optic atrophy (“Band” optic atrophy)**
 - Normally optic disc is paler at the temporal aspect; in case of **optic chiasmal lesions** the nasal aspect of the

disc also becomes pale – result is a white/pale “**bow-tie**” kind of **optic atrophy in both discs** with the knot of the tie at the centre of the disc.

- In **retrochiasmal pre-geniculate optic tract lesions**, a ‘diffuse’ kind of optic atrophy occurs in the ipsilateral eye and a typical ‘**bow-tie**’ optic atrophy in the contralateral eye.

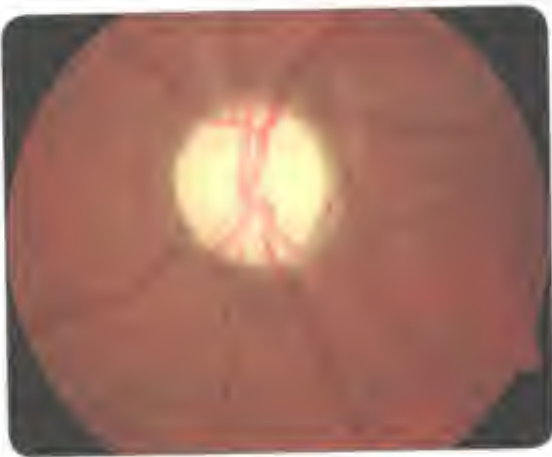


Fig. 21.51: Primary optic atrophy—reduction in number of small vessels on the disk

OPTIC NEUROPATHIES

Anterior Ischemic Optic Neuropathy (AION)

- **AION** is a segmental or generalized infarction of the anterior part of the optic nerve, caused by **occlusion of short posterior ciliary arteries.**
- Etiology:
 - **Non-arteritic AION:** MC entity; usually results from **atherosclerotic changes** in blood vessels.
 - **Arteritic AION:** Occurs in/w **giant cell arteritis** (see below).
 - **AION due to miscellaneous causes:** Collagen vascular disorders (PAN, SLE), emboli, malignant hypertension, migraine, and severe anemia.

Non-Arteritic AION (NAION)

- **Monocular, painless, sudden, marked visual loss**, with NO premonitory symptoms.
- Typical visual field defect is an **altitudinal hemianopia**, mainly **inferior half**.
- Ophthalmoscopy shows **sectorial edema with a hyperemic disc** and splinter hemorrhages.
- Contralateral disc is small and congested usually – “**disk-at-risk**”.

- **Color vision is impaired** in proportion to the level of visual acuity. This is in contrast to optic neuritis where color vision is severely impaired irrespective of the level of visual acuity.
- **Investigations:** blood glucose, lipid profile, factors affecting viscosity (fibrinogen and packed cell volume).
- Treatment is of any underlying disease and smokers should be advised to **stop smoking**. Long-term low dose aspirin.
- **Prognosis:** is **much better** than in arteritic AION. In most patients there is NO further loss of vision.
- One-third of patients develop AION in the opposite eye within several months or years. In this situation, optic atrophy in one eye and disc edema in the other eye gives rise to the so-called "**pseudo-Foster-Kennedy**" syndrome.

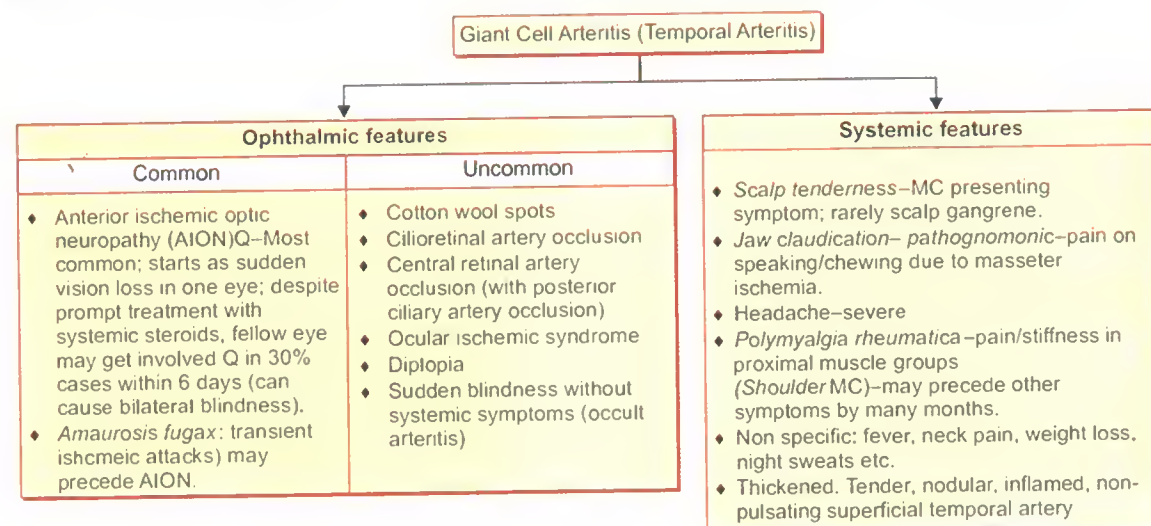
Arteritic AION

- This affects 25% of patients with untreated **giant cell arteritis** (GCA, temporal arteritis).

- Monocular, painless, sudden, marked visual loss, **WITH** premonitory symptoms like periocular pain and transient blurring of vision.
- See below for details about GCA.

GIANT CELL ARTERITIS

- Almost exclusively in individuals > **50 years** (around **70–80 years**).
- **Women** > Men affected and **Whites** > Blacks affected
 - **Granulomatous necrotizing arteritis** with predilection for **large and medium sized arteries** (superficial temporal, ophthalmic, posterior ciliary and proximal vertebral).
 - **Intracranial arteries are usually SPARED** (since they possess little elastic tissue).
 - **ESR+ ↑↑↑** often > 60 mm/hr. (20% of GCA may have normal ESR)
 - **CRP ↑↑, Platelet counts ↑↑**
 - Temporal artery biopsy – **diagnostic**



- **Complications of GCA:** Dissecting aneurysms, aortic incompetence, MI, ARI, brainstem stroke
- **Treatment of GCA:** systemic **steroids**.

Toxic Optic Neuropathy

- **Etiology:** Tobacco, alcohol, methyl alcohol, Vitamin B1 (thiamine) deficiency, Vitamin B12 deficiency, Drugs (INH, ethambutol, chloramphenicol, digitalis, streptomycin, chlorpropamide, ethchlorvynol, disulfiram and lead).

- **Signs:** painless progressive **bilateral** loss of vision; bilateral **centrocecal** scotomas.

EXTRA EDGE

Methyl alcohol poisoning results from drinking methylated spirit (mixed with country liquor). Methyl alcohol is oxidized to formic acid and **formaldehyde**, in the vitreous, causing destruction of retinal ganglion cells resulting in **total bilateral optic atrophy**. **Sudden complete blindness** is usually noticed after 2–3 days when the stupor wears off. Fundus exam in early cases reveals mild disc edema and markedly narrowed blood vessels. Finally **bilateral primary optic atrophy** ensues.

Leber's Hereditary Optic Neuropathy (LHON)

- **Painless progressive visual loss in one** and then the **other eye within days to months of each other**.
- **Mild disc edema** progressing to **optic atrophy over weeks**; small telangiectatic blood vessels near disc; occurs in young men aged 15–30 years; vision 6/60 to counting fingers; centrocecal scotoma
- Transmitted by **mitochondrial DNA (mtDNA)**; transmitted by mother to all offsprings.
- Genetic testing for most frequent base-pair nucleotide substitutions in the mitochondrial gene for the NADH dehydrogenase protein.
- Increased incidence of **cardiac conduction defects**.

EXTRAOCULAR MUSCLE PALSIES

Oculomotor Nerve Palsy (Third Nerve Palsy)

- Oculomotor N palsy
 - **Ptosis** (paralysis of levator palpebrae superioris),
 - **Mydriasis** (paralysis of sphincter pupillae),
 - **Restricted ocular movements** in all directions except outwards (due to lateral rectus);
 - Mild **exophthalmos/proptosis** (due to loss of ocular muscle tone)
 - In complete III N palsy, there is **ptosis which prevents diplopia**. With the eyelid raised, there IS diplopia which is **crossed** (heteronymous).
- **Isolated third nerve palsies are commonly basilar due to**
 - **Aneurysm of the posterior communicating artery** at its junction with the internal carotid artery; typically presents as **acute, painful third nerve palsy with involvement of the pupil**.
 - **Head trauma** resulting in extradural or subdural hematoma, may cause a tentorial pressure cone with downward herniation of the temporal lobe. This compresses the third nerve as it passes over the tentorial edge, initially causing irritative miosis followed by mydriasis and total third nerve palsy.
- **Pupil sparing third nerve palsy:**
 - MC in **diabetes and hypertension**

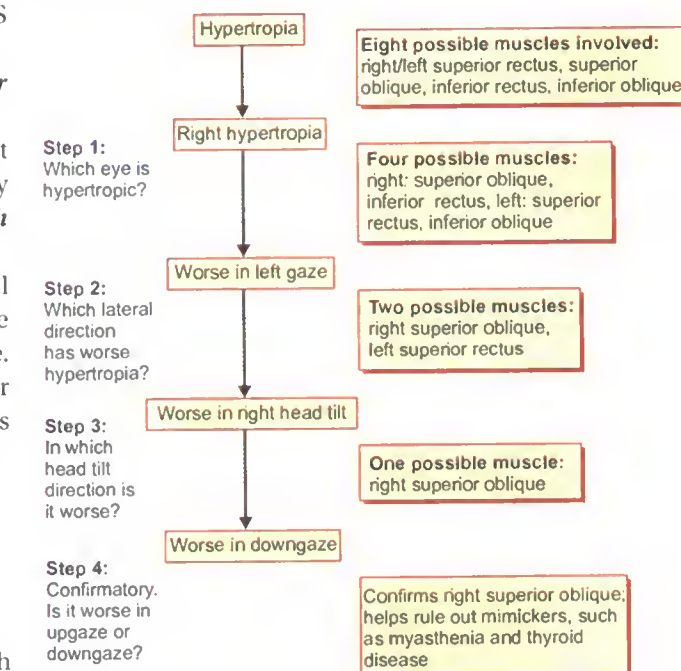
Abducens Nerve Palsy (Sixth Nerve Palsy)

- **Lateral rectus** muscle is paralyzed
- Hence, **esotropia/convergent squint** is present with limitation of movement outwards and the face is turned towards the paralyzed side.
- Homonymous (**UNCrossed**) **diplopia** occurs on looking to the paralyzed side.

Trochlear Nerve Palsy (Fourth Nerve Palsy)

- **Superior oblique** muscle is paralyzed.
- Congenital
- Acquired: Idiopathic (MC cause); Trauma (2nd MC cause); DM and HTN (cause isolated fourth N palsy)
- Clinical Features of Trochlear N palsy:
 - **Vertical diplopia** that is **worse on downgaze** and on **reading or looking down or going down the stairs** and **vertigo** is a prominent symptom.
 - Diplopia is also worse in gaze away from side of affected muscle
 - Head tilde away from affected side and chin depressed (to reduce the diplopia)
 - Ipsilateral hypertropia that increases on contralateral gaze
 - Hypertropia of affected eye with limitation of movement downward and towards the sound side.
 - Hypertropia also increases on tilting the head towards the side of hypertropia. (positive head tilt test)
 - Homonymous (**UNCrossed diplopia** occurs on looking down).

Parks-Bielschowsky Three-Step Test



Before going on to the actual test—you need to know about the **synergists**—try understanding the theory of 3-step test—then directly apply the “shortcut” mentioned below.

- **Synergists** are muscles of the *same eye* that move the eye in the *same* direction.
 - For example, the **right superior rectus** and **right inferior oblique** act synergistically in **elevation**.
 - Similarly, the **right inferior rectus** and **right superior oblique** act synergistically in **depression**.
 - Similarly, the **left superior rectus** and **left inferior oblique** act synergistically in **elevation**.
 - Similarly, the **left inferior rectus** and **left superior oblique** act synergistically in **depression**.
- **PARK - 3-Step Test:** This test is done to isolate one paretic/weak muscle in acute onset vertical diplopia.
- **Step 1:** Which eye is **HYPERtropic** in primary position?
 - Ex: **Right Hypertropia:** this means either the depressors of the right eye (RIR, RSO) are weak (causing right eye to move up) or the elevators of the left eye (LSR, LIO) are weak (causing the left eye to be hypotropic—makes the right eye 'appear'—hypertropic)—So basically in step 1, you determine, "which eye is **HYPERtropic**".
- **Step 2:** Which lateral direction (right gaze or left gaze) worsens the hypertropia?
 - **REMEMBER: AS A RULE** - In superior oblique palsies the hypertropia is "**Worse On Opposite Gaze** (**WOOG**)" - Thus if the **right hypertropia is worse on left gaze** - it means the weak muscle could be Right Superior Oblique or Left superior rectus (since these two muscles have the greatest vertical section in left gaze - No need to remember that). Here you have almost confirmed that it is 'right superior oblique'.
- **Step 3:** Bielschowsky head tilt test: In superior oblique palsy, the hypertropia is **Better On Opposite Tilt** (**BOOT**). So if the **right hypertropia lessens/better on left head tilt and worsens on right head tilt** - it is

confirmed that it is "**Right superior oblique palsy**".

SHORTCUT!

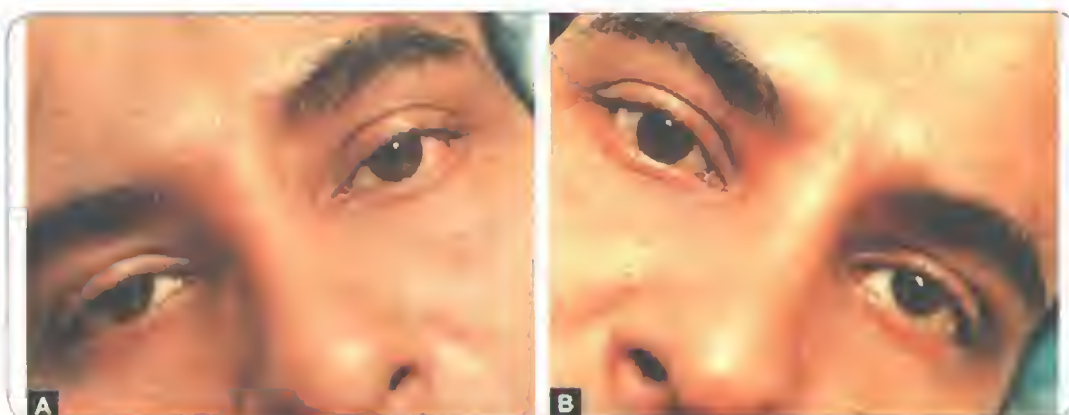
- If it is difficult for you to understand the entire theory above - just use these below points.
- Park-3-step test is almost always done to **confirm 4th cranial nerve (trochlear) - superior oblique palsy**.
- **Compensatory head tilt** is to the **opposite side** in Sup Oblique palsy - thus left sup oblique palsy will have head tilt to right and vice versa.
- **WOOG**—In Sup Obl palsy, hypertropia is **Worse On Opposite Gaze**.
- **BOOT**—In superior oblique palsy, the hypertropia is **Better On Opposite Tilt**.

NOW, try below question yourself by applying the above SHORTCUT RULES.

"A 12-year-old boy comes into room with left sided head tilt, on correcting that he has right sided hypertropia, which increases on left gaze and tilting the head towards right. Which muscle is affected?" (AIIMS May 2008)

Explanation

- Boy came in with left compensatory head tilt - so most likely it is a right superior oblique palsy.
- Also given is that "on correcting the head tilt (means, in primary position) he has right hypertropia which increases in left gaze" - "**WOOG**" - so again most likely right superior oblique palsy (since right hypertropia worsens in left gaze - opposite gaze).
- Also given is that "Right hypertropia increases in Right head tilt (meaning right hypertropia is better in left - i.e. opposite head tilt - **BOOT**)" - so it is confirmed that it is right superior oblique palsy!



Figs. 21.52A and B: Bielschowsky's head tilt test in left superior oblique palsy



Fig. 21.53: Right third nerve palsy



Fig. 21.54: Right sixth nerve (lateral rectus) palsy
Note—absence of abduction in right eye

Syndromes with Ocular Muscle Palsies

- **Benedikt's** Ipsilateral oculomotor palsy and contralateral tremors/chorea/athetosis. (**Red nucleus injury**)
- **Nothnagel's** Ipsilateral oculomotor palsy and contralateral cerebellar ataxia (**superior cerebellar peduncle injury**)
- **Claude's** Incorporates features of both aforementioned syndromes, due to injury to both areas
- **Weber's** Ipsilateral oculomotor palsy with contralateral hemiplegia (**cerebral peduncle injury**)
- **Foville** Lateral gaze palsy, ipsilateral facial palsy, contralateral hemiparesis (**dorsal pontine injury**)
- **Millard Gubler** Similar to the above syndrome, but lateral rectus weakness only (**ventral pontine injury**)

Cortical Blindness (Visual Cortex Disease, Striate/ Occipital Cortex, Area 17)

- Formed **visual hallucinations**, particularly involving hemianopic field.
- **Denial of blindness** (**Anton syndrome**)
- **Riddoch phenomenon:** ability to perceive moving, but not static visual targets.
- **Congruous homonymous hemianopia** with **macular sparing** (**anterior occipital cortex**) or **congruous homonymous macular defect** (**tip of occipital cortex**).
- Direct and Consensual light reflexes present—i.e. **normal pupillary reflexes**.

EXTRA EDGE

Charles Bonnet syndrome: Significant visual impairment due to pathology anywhere along the visual pathways from the eye to the primary visual cortex may result in emergence of complex visual hallucinations.

Conjugate Eye Movements

Saccades

Function: Fixating eye movements to place the object of interest on the fovea **rapidly** or to **move the eyes from one object to another**.

Pathway: for horizontal saccades originates in the premotor cortex (**frontal eye fields**); fibres pass to the contralateral horizontal gaze centre in the PPRF. Each frontal lobe therefore initiates contralateral saccades.

Contd

Contd...

Smooth pursuit movements

Function: to maintain fixation on a target once it has been located by the saccadic system; movements are **slow and smooth**.

Pathway: originates in the **prestriate cortex of the occipital lobe**. The fibres descend and terminate in the ipsilateral horizontal gaze centre in the PPRF. Each occipital lobe hence, controls pursuit to the ipsilateral side.

Non-optical (vestibular) reflexes

Function: is to maintain eye position with respect to any changes of head and body position.

Pathway: originates in the labyrinths and proprioceptors in the neck muscles which mediate information about head and neck movements; afferent fibres synapse in the vestibular nuclei and pass to the horizontal gaze centre in the PPRF.

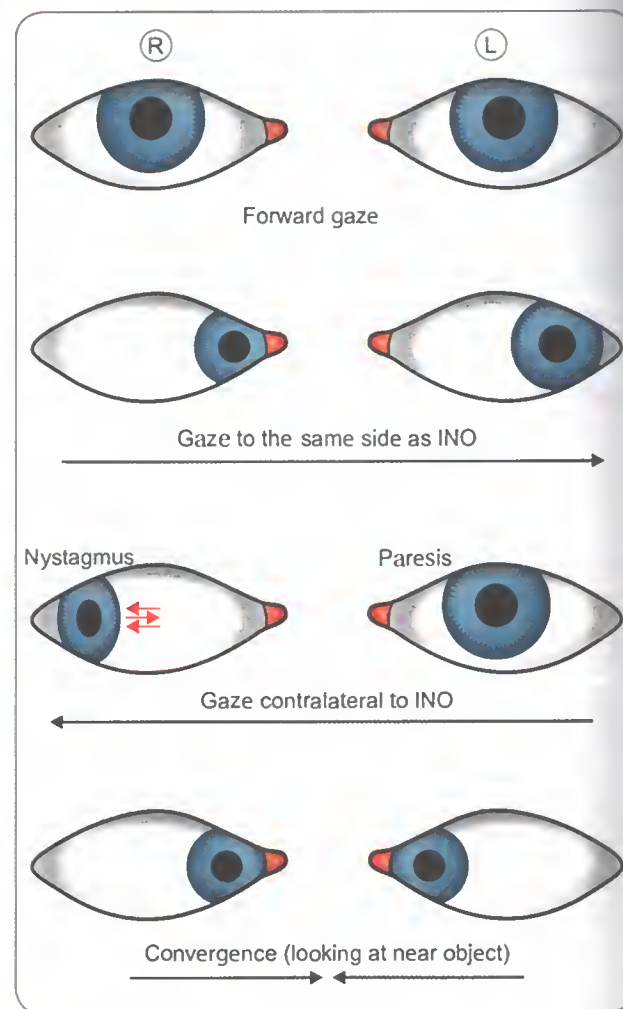
Horizontal Gaze Palsy**Anatomy**

- **Horizontal eye movements** are generated from the horizontal gaze centre in the Para Pontine Reticular Formation (PPRF). From here motor neurons connect to the **ipsilateral VI nerve nucleus** that innervates the lateral rectus.
- From the VI nerve nucleus, internuclear neurons cross the midline at the level of the pons and pass up the contralateral medial longitudinal fasciculus (MLF) to synapse with the motor neurons in the medial rectus subnucleus in the III N complex which innervates the medial rectus.
- Stimulation of the PPRF on one side therefore causes a conjugate movement of eye to the same side.

Diagnosis

- **PPRF lesion** gives rise to ipsilateral horizontal gaze palsy with inability to look in the direction of the lesion.
- **MLF lesion** is responsible for **INO** (**internuclear ophthalmoplegia**).
- Etiology of **bilateral INO** is **MC multiple sclerosis**.
- Damage to fibers carrying the conjugate signal from abducens interneurons to the contralateral medial rectus motoneurons results in a **failure of adduction on attempted lateral gaze**.
- A **left INO** is characterized by:
 - Straight eyes in primary position
 - Defective left adduction and ataxic nystagmus of the right eye on right gaze.

- Left gaze is normal
- Convergence is intact if lesion is discrete; this may help to differentiate INO from myasthenia.
- Vertical nystagmus on attempted up gaze.
- **"One and half syndrome"** = **PPRF + MLF combined lesions**; characterized by ipsilateral gaze palsy and INO so that only residual movement is abduction of the contralateral eye which also exhibits ataxic nystagmus

**Fig. 21.55:** Left internuclear ophthalmoplegia**Vertical Gaze Palsy**

- **Vertical eye movements** are generated from the vertical gaze centre (**rostral interstitial nucleus of the MLF**) in the midbrain just dorsal to the red nucleus. Two syndromes are given below.

Parinaud's dorsal midbrain syndrome

- Straight eyes in primary position
- Supranuclear upgaze palsy
- Defective convergence
- Large pupils with light near dissociation
- Lid retraction (Collier sign)
- Convergence-retraction nystagmus.

Progressive supranuclear palsy (Steele Richardson synd.)

- Severe degenerative disease of old age characterized by
- Supranuclear gaze palsy initially affecting downgaze
- Later upgaze also affected
- Finally global gaze palsy develops
- Pseudobulbar palsy
- Extrapyrmidal rigidity, gait ataxia and dementia
- Paralysis of convergence.

MORE HIGH-YIELD POINTS IN NEUROLOGY

- **CNS germinoma:** MC tumor of the pineal gland (pineal germinoma - can lead to obstructive hydrocephalus and Parinaud's syndrome) and also can occur in the suprasellar region (suprasellar germinoma - diabetes insipidus and hypopituitarism). on CT scan appears as homogenous hyperdense lesion.
- Autoregulation of Cerebral blood flow occurs over a mean arterial pressure of 50-150 mm Hg.
- On a **CT scan** of brain hematomas are easily diagnosed. They appear
 - **hyperdense** if Hb > 9 mg/dl;
 - **hypodense** if Hb < 9 mg/dl;
 - **isodense** if Hb = 9 mg/dl.
- Patients who are **at risk of posttraumatic epilepsy** include those with:
 - Intracranial hematoma
 - Supratentorial depressed skull fracture
 - Brain injury with focal neurologic signs or posttraumatic amnesia for more than 24 hours
 - Combat missile wounds.
- **Phenytoin** is used for the **prophylaxis** of posttraumatic epilepsy.
- For **spinal cord injury methylprednisolone** administered **within 8 hours** has been shown to be effective
- For **hypertensive intracranial hemorrhage, unenhanced CT scan is the study of choice**.
- **Telangiectasias in the brain** are more frequently in the **pons** and unlikely to bleed.
- In cases of brain herniation, pupillary dilatation is ipsilateral in 80%. So it is much more reliable than hemiparesis in localizing the side of lesion. In 20%, pupillary dilatation is on the opposite side and hemiparesis is ipsilateral to the lesion - a **false localising sign** - **Kernohan notch** (Kernohan-Woltman notch phenomenon).
- Diseases Associated With Neuropathic Joint Disease (Charcot's joints): Diabetes mellitus; Syringomyelia;

- **Tabes dorsalis;** Meningomyelocele; **Amyloidosis;** Congenital indifference to pain; Leprosy.
- **Central pontine myelinolysis:** Acute paralysis, dysarthria, dysphagia, diplopia and loss of consciousness; Commonly caused by very rapid correction of hyponatremia.
- **Burrholes:** The standard placement for the **first exploratory burr hole** is in the **left temporal** region since dominant **temporal lobe decompression is usually the most urgent priority** in acute cerebral herniation. In the absence of CT scan or other localization, burr holes are initially placed on the **side ipsilateral to the larger pupil**. If the pupils are equal or there is no hemiparesis, the side of obvious external trauma should be chosen and the burr hole should be placed next to, not within, a skull fracture.
- **Ocular bobbing** is a distinctive eye movement disorder seen in patients with **pontine dysfunction**.
- **Serotonin and dopamine** play an important role in **pleasure seeking**; **Nucleus accumbens** is referred to as the **brain's pleasure center**.
- In neuroscience, **long-term potentiation (LTP)** is a persistent strengthening of synapses based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons. The opposite of LTP is long-term depression, which produces a long-lasting decrease in synaptic strength.
- Subdural empyema (i.e. abscess) is an intracranial focal collection of purulent material located between the dura mater and the arachnoid mater; Causes: otitis media, mastoiditis, meningitis, sinusitis, skull osteomyelitis.
- **Diffuse axonal injury (DAI):** A shearing type of **brain injury** seen in severe **head trauma**. The cut end of axons appear as **"retraction balls"**; these represent egress of excess cytoplasm from at end of axons. **MRI** is the inv. of choice **Small petechial hemorrhages** located at **gray-white matter junction** and corpus callosum are characteristic.
- The **locked-in syndrome (pseudocoma)** describes patients who are awake and conscious but selectively deafferented, i.e., have no means of producing speech, limb or facial movements. **Acute ventral pontine lesions** are its **MC cause**.
- **SPIKES** approach is a protocol for disclosing unfavorable information—"breaking bad news"—to **cancer patients/critically ill patients** about their illness. The protocol (SPIKES) consists of six steps: S = "Setting Up"; P = "Perception"; I = "Invitation"; K = "Knowledge"; E = "Empathizing and Exploring"; S = "Strategy and Summary".

RESPIRATORY SYSTEM

BASICS

Dyspneas

- **Orthopnea** (*dyspnea on recumbency*) and nocturnal dyspnea are seen in *asthma*, *LVI*, *GERD* (gastroesophageal reflux disease), *obstructive sleep apnea*.
- **Platypnea** (*dyspnea that worsens in upright position*) is *a/w* deficient abdominal musculature, AV malformations at lung bases.
- **Trpeopnea**: Dyspnea that occurs *only in lateral decubitus position* most often in patients with *heart disease*.
- **Constant dyspnea** is mostly due to *COPD* but also seen in *ILD* (pulm. fibrosis).

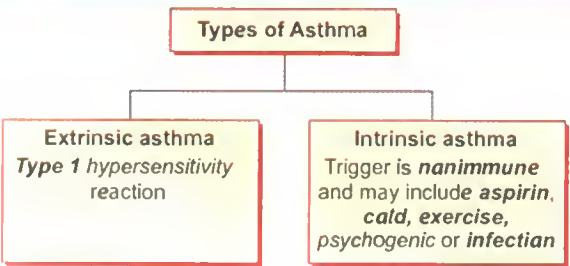
Sputum Types

<i>Pink frothy</i> sputum	<i>Pulmonary edema</i>
Sputum containing <i>Charcot Leyden crystals/Curschmann's spirals</i>	<i>Branchial Asthma</i>
<i>Currant Jelly</i> sputum	<i>Klebsiella pneumonia</i>
<i>Green sputum</i>	<i>Pseudamanas</i>
<i>Rusty sputum</i>	<i>Pneumococcal pneumonia</i>
<i>Albuminoid sputum</i>	<i>Pulmonary edema</i>

Crackles

- **Early inspiratory** crackles: Small airway disease such as *bronchiolitis*
- **Mid-inspiratory** crackles: *Pulmonary edema*
- **Late inspiratory** crackles: *Pulmonary fibrosis (fine)*
- Crackles *throughout inspiration and expiration*: *Bronchiectasis*.

ASTHMA



Pathology of Asthma

- *Bronchial wall edema* and development of inflammatory infiltrate with increased number of *eosinophils*, thickening of basement membrane, bronchial smooth muscle hypertrophy and hyperplasia, and hypertrophy of submucosal mucus glands.
- **Microscopically**: Seen within the airways are:
 - Whorled mucus plugs (*Curschmann's spirals*) and
 - Crystalloid debris of eosinophil membranes (*Charcot-Leyden crystals*).
- **Airway Hyper-responsiveness** (AHR) is the *characteristic physiologic abnormality* of asthma and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways.
- The increased AHR is normally measured by *methacholine or histamine challenge* with calculation of the provocative concentration that reduces FEV1 by 20% (PC20).

Clinical Features

- Classic symptoms of asthma are *wheezing, dyspnea, and coughing*.
- Symptoms may be *worse at night*, and patients typically *awake in the early morning hours*.
- Increased mucus production (typically tenacious mucus that is difficult to expectorate) in some patients.
- *Prolonged expiration* and *expiratory rhonchi* throughout the chest on physical examination.

Samter's triad

- Bronchial asthma +
- Nasal allergy/polypsis +
- Hypersensitivity to aspirin

Labs

- **Reduced FEV1, FEV1/FVC ratio, and PEF**(Peak Expiratory Flow Rate) seen on simple spirometry (signs of airflow limitation).
- **Diurnal variation in PEF**(i.e. the difference between the morning and evening measurements) of greater than 15-20% has been used as *a defining feature of asthma*.
- **Bronchodilator reversibility test**: *Reversibility* of airflow *obstruction*, either spontaneously or following *bronchodilator* therapy.

Immediate Assessment of Acute Severe Asthma

Acute severe asthma
<ul style="list-style-type: none">• PEF 33-50% predicted (< 200 l/min)• Respiratory rate ≥ 25/min• Heart rate ≥ 110/min• Inability to complete sentences in 1 breath.
Life-threatening features
<ul style="list-style-type: none">• PEF 33-50% predicted (< 100 l/min)• SpO₂ < 92% or PaO₂ < 8kPa (60 mm Hg) (especially if being treated with oxygen)• Normal PaCO₂• Silent chest• Cyanosis• Feeble respiratory effort• Bradycardia or arrhythmias• Pulsus paradoxus• Hypotension• Exhaustion• Confusion• Coma
Near fatal asthma
<ul style="list-style-type: none">• Raised PaCO₂ and/or requiring mechanical ventilation with raised inflation pressures.

Management of Acute Severe Asthma Includes

- *High flow oxygen by face mask*
- *Nebulized short acting β-2 agonist (salbutamol or terbutaline)*
- *High dose corticosteroids (prednisolone oral or IV hydrocortisone)*
- *Nebulized ipratropium bromide*
- *IV aminophylline/theophylline*.

Treatment of Asthma

- Anti-asthma drugs have been discussed in *pharmacology chapter (Pg 334)*.

D/D OF COMMUNITY ACQUIRED PNEUMONIAS

Organism	Clinical features
Common organisms	
<i>Streptococcus pneumoniae</i>	MC cause ; MC in <i>winter</i> ; young to middle aged patients; rapid onset high fever, <i>pleuritic</i> chest pain, <i>herpes labialis</i> , ' <i>rusty sputum</i> '; <i>Sir William Osler</i> (father of modern medicine) called Strep pneumonias as the " <i>captain of the men of death</i> "
<i>Mycoplasma pneumoniae</i>	Atypical pneumonia , children and young adults; epidemics occur every 3-4 years, rare complications – hemolytic anemia (<i>cold agglutinins</i>), erythema nodosum, Steven Johnson syndrome, myocarditis, pericarditis, Gillain Barre syndrome

Contd...

Contd...

Organism	Clinical features
<i>Chlamydia pneumoniae</i>	Large scale epidemics or sporadic, often self-limiting mild illness , headaches, usually diagnosed on <i>serology</i>
<i>Legionella pneumophila</i>	Recent foreign travel ; atypical pneumonia, local epidemics around point source (ex: cooling tower, aerosolized water); variety of clinical features such as <i>headache, confusion, malaise, myalgia, high fever, diarrhea</i> ; Labs – <i>hyponatremia</i> , elevated liver enzymes, hypoalbuminemia, elevated creatine kinase, CXR appearances may be slow to resolve
Uncamman organisms	
<i>Hemophilus influenzae</i>	Often underlying lung disease (COPD, bronchiectasis)
<i>Klebsiella</i>	MC in men and <i>alcoholics</i> , ' <i>currant jelly</i> ' sputum, upper lobe involvement typical, low platelet count and leucopenia
<i>Staphylococcus aureus</i>	Coexistent skin infections and often preceded by influenza (pastviral) ; CXR – multilobar shadowing, <i>cavitation</i> , pneumatoceles , abscesses (<i>empyema</i>), pneumothorax; dissemination – brain abscess or endocarditis; mortality -30%
<i>Chlamydia psittaci</i>	Contact with birds (pigeons etc.); low grade fever, long illness, <i>hepatosplenomegaly</i>
<i>Coxiella burneti</i> (fever)	Male sex, farm or abattoir contact; chronic course; influenza like illness
<i>Nosocomial</i> (hospital acquired)	Gram negative rods, staphylococcus
<i>Aspiration</i> Pneumonia	Anaerobes

EXTRA EDGE

- **CURB-65 Score for Pneumonia Severity**: Estimates mortality of community-acquired pneumonia to help determine inpatient vs. outpatient treatment. The CURB-65 scores range = 0 to 5. *Inpatient admission* with consideration for *ICU admission* with score of 4 or 5
- **Confusion**
- **BUN** > 19 mg/dL (> 7 mmol/L)
- **Respiratory Rate** ≥ 30
- **Systolic BP** < 90 mm Hg or **Diastolic BP** ≤ 60 mm Hg
- **Age** ≥ 65
 - Pneumonia is an *infection of the pulmonary parenchyma*.

Few other Pneumonia History/Clinical Hints

MC cause of Pneumonia in children	Viral
MC cause of hospital acquired pneumonia	Enteric gram neg. bacilli
Cystic fibrosis , Immunocompromized/chronically ill patients	<i>Pseudomonas aeruginosa</i>
Exposure to bats or birds	<i>H. capsulatum</i>
Exposure to rabbits	<i>Francisella tularensis</i>
Exposure to sheep, goats, parturient cats	<i>Coxiella burnetii</i>
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Alcoholics	<i>Klebsiella</i>
"Pneumonia alba – white lung"	congenital syphilis
Primary giant cell pneumonia (Hecht's pneumonia)	Measles

Course of Uncomplicated Lobar Pneumonia

- **Congestion** predominates in the **first 24 hours**.
- **Red hepatization (consolidation)** is a picture of lung tissue with confluent acute exudation containing neutrophils and **red cells**, giving a **red**, firm **liver-like** gross appearance.
- **Grey hepatization** follows as the red cells disintegrate and the remaining fibrinosuppurative exudate persists, giving a grey brown gross appearance; **neutrophils predominate**.
- **Resolution** is the favorable final stage in which consolidated exudate undergoes enzymatic and cellular degradation and clearance' **macrophage** is predominant cell type. Normal structure is restored.

EMPHYSEMA (PINK PUFFER)

- **Emphysema** is the abnormal permanent enlargement of air spaces distal to the terminal bronchioles, with alveolar wall destruction and minimal fibrosis.
- **Pathology:** **Excess activity of protease and elastase** resulting in permanent enlargement of distal airspaces with destruction of alveolar walls; smoking inactivates α -1-AT.
- **Clinical features:** Dyspnea, ↓ FEV1, ↓ FVC, ↑ TLC, **Barrel chest**, hypoxia, **respiratory acidosis**, **pulmonary hypertension**, **cor pulmonale**, **increased lung compliance** (fibrosis has low lung compliance); **Chest is very quiet** without adventitious sounds.

- Diagnosis by **HRCT** scan; plain X ray is insensitive.
- In **cor pulmonale**, calculated measures of **RV function** (**TAPSE** = Tricuspid Annular Plane Systolic Excursion or the **Tei Index**) help in subjective assessments of RV function.

Types of Emphysema

- **Centriacinar emphysema**
 - Dilatation of respiratory bronchioles
 - Involves upper lobes and apices
 - Seen in **male smokers**.
- **Panacinar emphysema**
 - Uniform destruction and enlargement of acinus
 - More common in lower basal zones
 - Strong a/w **α -1-AT deficiency**.
- **Paraseptal emphysema**
 - Involves the distal acinus, sparing the proximal
 - Common adjacent to the pleura and adjacent to fibrosis or scars resulting in bullae and blebs which may lead to **spontaneous pneumothorax**.

EXTRA EDGE

- In emphysema, **decreased expiratory flow rates (FEV1)** are largely due to **loss of elastic recoil** of the lung resulting in the following:
 - Lower driving pressure for expiratory airflow
 - Loss of radial traction on the airways provided by supporting alveolar walls thus promoting airway collapse during expiration
- Radiology of emphysema has been discussed in radio-diagnosis chapter (Pg 1175).

CHRONIC BRONCHITIS (BLUE BLOATER)

- **Definition:** Persistent **cough with sputum production for at least 3 months in at least 2 consecutive years**.
- **Pathology:** Chronic airway irritation by tobacco smoke → **mucus hypersecretion** with mucus gland hypertrophy; **goblet cell metaplasia** in bronchiolar epithelium, bronchiolitis.
- **Clinical features:** Productive cough, wheezing, cyanosis, rales, cor pulmonale.
- **Reid index:** is the ratio of thickness of submucosal glands to that of bronchial wall. In persons without a history of chronic bronchitis this ratio is 0.44 ± 0.09 , whereas in those **with chronic bronchitis** the mean ratio is 0.52 ± 0.08 .

EXTRA EDGE

- Global Initiative for Obstructive Lung Disease (GOLD) is an international collaboration of experts in COPD; the GOLD guidelines for severity of COPD is given below.

GOLD Stage	COPD severity	FEV1/FVC ratio	FEV1 range
I	Mild	< 0.7	> 80% normal
II	Moderate	< 0.7	50-79%
III	Severe	< 0.7	30-49%
IV	Very Severe	< 0.7	<30% of normal OR < 50% of normal with chronic respiratory failure present

BRONCHIECTASIS

- Chronic necrotizing infection of bronchi → **permanently dilated bronchi, purulent sputum, recurrent infections, hemoptysis**
- A/w **cystic fibrosis, poor ciliary motility**.
- **Kartagener's syndrome**
 - **Bronchiectasis**
 - **Sinusitis**
 - **Situs inversus**
- Patients can develop **Aspergillosis**.
- **Gold standard** investigation – **HRCT** (High Resolution CT)
- **Nodular bronchiectasis** is seen in infection with Myco. avium complex (MAC).

TUBERCULOSIS

Mycobacterium tuberculosis (Koch's bacillus)

- Gram + rod, acid fast.
- High cell wall content of **mycolic acid** – leads to **acid fastness** and also stains **red on Zeihl Neelsen stain**.
- **Obligate aerobe** - requires **Lowenstein Jensen (L-J) medium** for growth
- Doubling time = **18 hours** (vs 20 minutes for E.coli), hence can take up to **8 weeks for cultures** to grow
- Produces **niacin**.
- Virulence factors: **Cord factor** allows growth in extended chains.
- Mycolic acids are linked to underlying **arabinogalactan** and **peptidoglycan** – confers very low permeability of the cell wall, thus **reducing the effectiveness of most antibiotics**.
- Cell wall **lipoarabinomannan**, is involved in the pathogen-host interaction and **facilitates the survival of M. tuberculosis within macrophages**.

Named lesions in TB

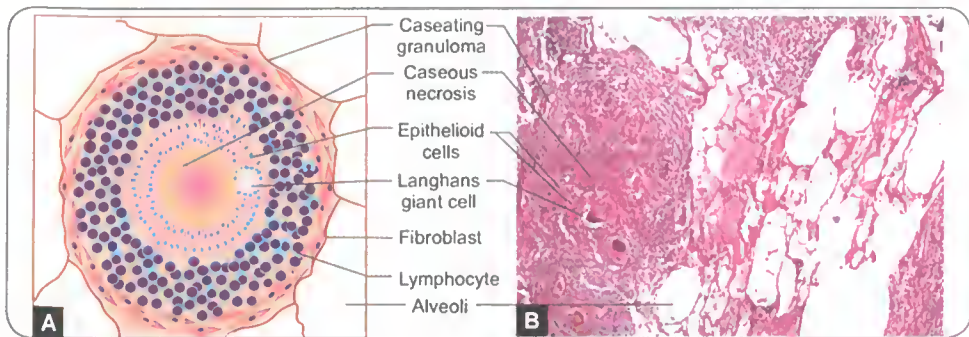
- **Puhl's lesion:** is the isolated lesion of chronic pulmonary TB in apex of lung.
- **Assman's focus:** Infraclavicular lesion of chronic pulmonary TB
- **Rancke complex:** Combination of calcified peripheral lesion (Primary/Ghon complex) and calcified hilar nodes.
- **Rasmussen aneurysm:** Hemoptysis, in TB, may also result from rupture of a aneurysm of pulmonary artery within a cavity.
- **Rich focus:** TB granuloma on the cortex of brain that ruptures into subarachnoid space.
- **Simmond's focus:** Healed foci of TB in the liver.
- **Welgert focus:** Healed foci of TB in intima of blood vessels.

Differences between **Primary (Childhood) TB** and **Secondary TB (Adult TB)**

Primary TB (Childhood TB)	Secondary TB (adult-type, reactivation, postprimary disease)
Soon after initial infection with TB bacilli	Endogenous reactivation of latent infection
Often seen in children	Often seen in adults
Involves middle and lower lung zones	Involves apical and posterior segments of the upper lobes and superior segments of the lower lobes
Primary subpleural granuloma in the inferior upper lobe/superior lower lobe region (Ghon focus) + draining hilar/bronchial lymph nodes = Ghon complex . In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (progressive primary TB).	Leads to caseous necrosis and formation of Cavitations (mainly) Fibrosis Calcifications
Mostly non-infectious	Highly infectious
Sputum positivity rare	Sputum for AFB common
Lymphadenopathy is significant (mediastinal or hilar)	No significant lymphadenopathy
Cavity rare or thin walled	Cavity common (thick walled)
Healing mainly by dystrophic calcification	Healing by fibrosis
Extrapulmonary complication is very common	Lesion is mainly localized to lungs
Spread by hematogenous, lymphatic and parenchymatous route	Spread is mainly bronchogenic inside the parenchyma . Extrathoracic spread is not documented

EXTRA EDGE

- In children, localized forms of illness, e.g., intrathoracic lymphadenopathy, and localized CNS disease has been reported to occur with greater frequency.
- Extensive epidemiologic studies show that **most children with typical tuberculosis rarely if ever infect other children or adults**. When children with TB cough, they **rarely produce sputum** and **lack the tussive force necessary to suspend the infectious particles in the air**. The risk of transmission from children is remote.
- **Massive life-threatening hemoptysis** can occur due to **Aspergilloma within a TB cavity**; it is an indication for surgery (lobectomy)
- Please go through the attached graphical/flowchart of pulmonary TB. These are quite self-explanatory and important from MCQ point of view.



Figs. 21.56A and B: Microscopic appearance of tuberculous lung. A. Diagrammatic; B. Photomicrograph. Central area of caseation surrounded by epithelioid and multinucleated giant cells

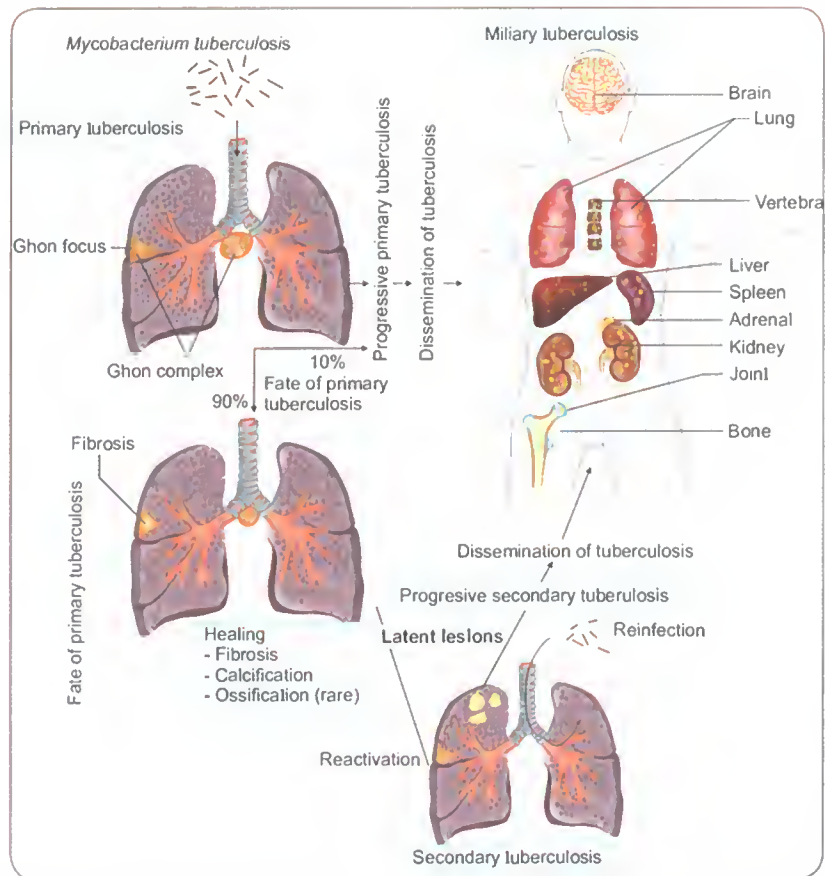


Fig. 21.57: Natural history and various stages of tuberculosis

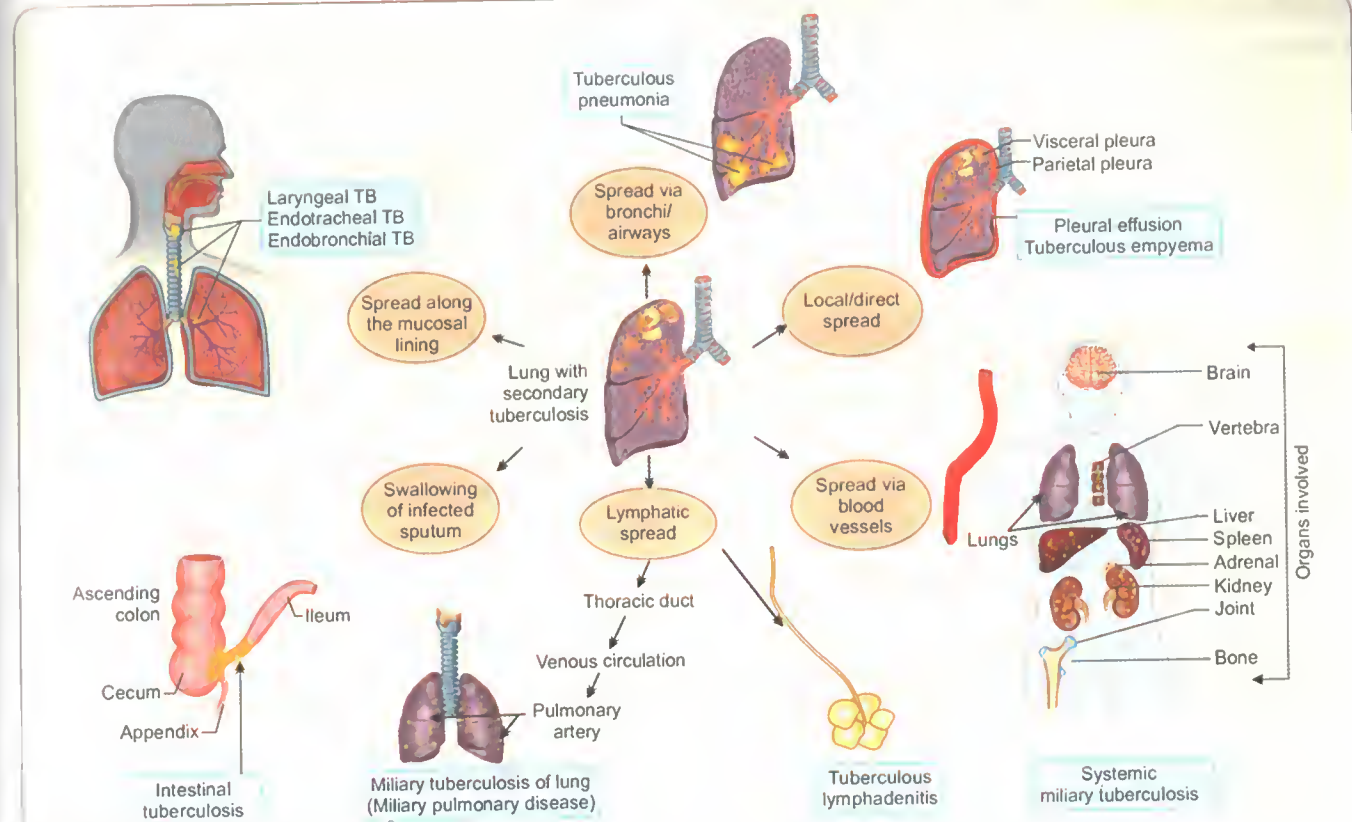


Fig. 21.58: Progress and complications of secondary tuberculosis of lung

EXTRAPULMONARY TB

- In order of frequency, the extrapulmonary sites MC involved in TB are the **lymph nodes**, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and **pericardium**. However, virtually all organ systems may be affected.

Lymph Node TB (Tuberculous Lymphadenitis)

- This is the **MC presentation of extrapulmonary TB**.
- **Matted** lymphnodal mass is the typical clinical feature.
- In later stages the mass may be cystic denoting an abscess - this abscess denotes underlying caseation and does not show any features of inflammation - hence called "cold abscess".
- Ultimately the abscess may burst forming a sinus.
- Diagnosis: culture of pus and biopsy of the lymph node.
- Treatment is mainly medical (course of ATT).

More High Yield about extrapulmonary TB

- **Indurated seminal vesicle** is seen in **genital TB**.

- TB of the upper airways (larynx, pharynx, and epiglottis) is usually a **complication of advanced cavitary pulmonary TB**.
- **Tuberculous pleural effusion:**
 - Fluid is straw colored;
 - It is an exudate
 - Protein concentration >50% of that in serum (usually ~4-6 g/dL),
 - A normal to low glucose concentration,
 - A pH of ~7.3 (occasionally <7.2), and
 - Lymphocytic predominance.
- **Tuberculoma:** MC site in brain is Posterior cranial fossa
- **TB pericarditis** is the **MC cause of pericardial calcification**.
- **Golf hole ureter** and **thimble bladder** are seen in TB urinary bladder.
- **Spine** is MC affected in **skeletal TB**.
- **Pott's disease** = tuberculous spine/spondylitis.
- Skeletal TB has been described in a detailed table in orthopedics chapter (Pg 739).

HYPERSENSITIVITY PNEUMONITIS (HP)

- A.k.a *extrinsic allergic alveolitis*, is a pulmonary disease that occurs due to *inhalational exposure* to a variety of *antigens* leading to an inflammatory response of the alveoli and small airways.
- *Fever and fatigue* can accompany respiratory symptoms (*dyspnea*).
- Main treatment is *avoidance* of antigen. See table below.

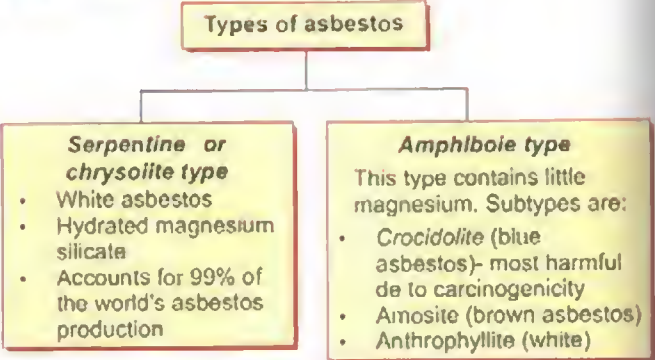
Disease	Antigen	Source
Bagassosis	Thermophilic actinomycetes, <i>T.socchari</i>	Sugarcane fibre (Bagasse)
Farmer's lung	Thermophilic actinomycetes (e.g., <i>Saccharopolyspora rectivirgula</i>); fungus	Grain, moldy hay, silage
Cheese washer's lung	<i>Penicillium casei</i> ; <i>Aspergillus clavatus</i>	Cheese
Malt warker's lung	<i>Aspergillus</i> species	Barley
Miller's lung	<i>Sitophilus granarius</i> (wheat weevil)	Wheat flour
Wine maker's lung	<i>Botrytis cinerea</i>	Grapes
Hot tub lung	<i>Cladosporium</i> species; <i>Mycobacterium avium</i> complex	Contaminated water, mold on ceiling
Detergent warker's lung	<i>Bacillus subtilis</i> enzymes	Detergent
Suberosis	<i>Penicillium glabrum</i> ; <i>Chrysomilia sitophila</i>	Cork dust

PNEUMOCONIOSIS (OCCUPATIONAL LUNG DISEASE)

- Particles > 5µ are filtered in upper airways and < 1µ can remain suspended and are exhaled.
- Particles 1–5µ (0.5–3 microns) settle in the alveoli as the most potentially dangerous particles.

Inorganic dusts	
Coal dust	: Anthracosis
Silica	: Silicosis
Asbestos	: Asbestosis
Iron	: Siderosis
Cotton dust	: Byssinosis ('Manday chest tightness')
Tobacco	: Tobaccosis

Asbestosis



- **Asbestos bodies:** Asbestos fibres coated with glycoprotein and endogenous hemosiderin to produce characteristic dumb-bell shaped asbestos bodies. These may be seen in sputum.
- **Ferruginous body** is an Iron protein complex coating inorganic particles such as asbestos, talc, mica and glass in the lung (*Asbestos body is also a ferruginous body*).

Asbestos Effects on the Respiratory Tract

- Pulmonary *fibrosis* - asbestosis
- Being in *pleural plaques* (often calcified -indicates past exposure; seen along parietal pleura of lower lung fields)
- *Pleural effusion* (benign or malignant) and diffuse pleural fibrosis
- *Mesothelioma*
- *Ca lung* (bronchogenic Ca)
- Ca larynx
- Interstitial lung disease

Silicosis

- Prolonged *inhalation of silica* (SiO₂ or *crystalline quartz*) produces a chronic, *nodular, dense pulmonary fibrosis*.
- CXR shows
 - 'snow-storm' appearance;
 - "egg shell" calcification of hilar nodes seen (In 20% of cases).
- Silicotics have greater risk of acquiring *pulmonary TB* (*silicotuberculosis*)

Coal Workers Pneumoconiosis

Anthracosis	Small <i>harmless accumulations</i> seen in the lungs of <i>urban dwellers/smokers</i> .
--------------------	--

Contd...

Contd...

Simple coal workers pneumoconiosis (CWP)	With prominent aggregations of coal dust-laden macrophages forming <i>coal macules</i>
Complicated CWP or Progressive massive fibrosis (PMF)	Severe fibrosis and scarring (" <i>black lung</i> "), causes disabling <i>respiratory insufficiency</i>
Caplan's syndrome	Seropositive <i>rheumatoid arthritis</i> + <i>PMF</i>

Berylliosis

- **Beryllium**—Used in the manufacture of *alloys, ceramics, or high-technology electronics*
- Commonly causes a *chronic granulomatous inflammatory disease resembling sarcoidosis*.
- May also produce an acute pneumonitis
- *Delayed hypersensitivity* (specific cell mediated immunity) to *beryllium* is present - tested by *beryllium lymphocyte proliferation test (BeLPT)*.
- Chronic beryllium disease (CBD) is one of the best studied examples of gene-environment interaction. Susceptibility to CBD is highly associated with *HLA-DP* alleles possessing a glutamic acid in position 69 of the beta chain.

PLEURAL EFFUSION

	Transudative pleural effusion	Exudative pleural effusion
Mechanism	• Due to either <i>increased hydrostatic pressure</i> or <i>decreased osmotic pressure</i> - due to <i>systemic factors</i> .	• <i>increased microvascular pressure</i> due to disease of the pleura itself or injury in the adjacent lung - <i>local factors</i> .
Causes	• Left ventricular failure (<i>MC cause</i>) • Cirrhosis • Nephrotic syndrome • Malnutrition	• TB • Pneumonia (para-pneumonic) • Viral infection • Malignancy • Pulmonary infarction/embolism • Subdiaphragmatic disorders (subphrenic abscess, pancreatitis etc.)

Exudative Pleural Effusion Criteria

Light's Criteria: Pleural fluid is an *exudate* if one or more of the following criteria are met:

- Ratio of pleural fluid *protein* to serum protein > 0.5
- Ratio of pleural fluid *LDH* and serum LDH > 0.6
- Pleural fluid LDH is > 2/3 normal upper limit for serum (> 200)
- Pleural fluid protein >30 g/L.

Pleural Fluid Analysis

Elevated amylase in pleural fluid	Decreased pleural fluid glucose
• Pancreatitis • Esophageal rupture • Malignancy • Mnemonic: " <i>PEM</i> "	• Bacterial infection (empyema) • Malignancy (eosinophilia) • Rheumatoid arthritis (cholesterol crystals) • Mnemonic: " <i>BMR</i> "
Hemorrhagic pleural effusion	Chylous pleural effusion
• Bleeding disorders • Malignancy • Trauma • Pulmonary infarction • Mnemonic: " <i>B-MTP</i> "	• Obstructed thoracic duct; • Filariasis • Malignant invasion • Trauma • Mnemonic: " <i>FMT</i> "

- *Minimal pleural effusion* is detected on CXR by *lateral decubitus position*.
- *Pleural biopsy* is done with *Abram's needle*.
- *Lymphocytes* are more in *TB pleural effusion*.
- *Thoracentesis* (pleural fluid drainage, pleural tap) indicated when CXR shows an *effusion > 10 mm thick (or about 100 ml)*.
- For pleural tap *patient is sitting and leaning forward* over a support; Site is in the *lower part of the 5th or 6th intercostal space* in the *posterior axillary or midaxillary line (or below the tip of scapula)*.
- Structures pierced by the needle in pleural tapping has been described in anatomy chapter under thorax (Pg 66).

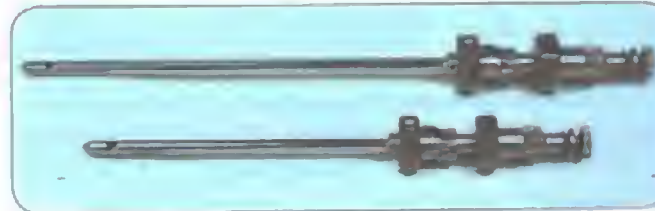


Fig. 21.59: Abram's pleural biopsy needle



Fig. 21.60: Chest X-ray showing right-sided pleural effusion. Right costophrenic angle blunting is seen with flattening of the diaphragm secondary to right-sided pleural effusion. Also note the infiltrations in the right upper lobe with pleural thickening in Koch's infection

SARCOIDOSIS

- **Lofgren's syndrome:** erythema nodosum, bilateral hilar adenopathy, arthritis.
- **Heerfordt-Waldenstrom syndrome (uveoparotid fever):** fever, parotid enlargement, anterior uveitis and facial N. palsy.
- **Lungs almost always involved (interstitial lung disease); lymphadenopathy** (paratracheal commonly, also mediastinal, cervical); skin (**lupus pernio**).
- **Diagnosis:** is by biopsy, ↑ ACE levels, hyperkalemia, lymphocytopenia
- **Chest X-ray:**

Stage I	Bilateral hilar lymphadenopathy (BHL)
Stage II	BHL + pulmonary infiltrates
Stage III	Pulmonary infiltrates without BHL
Stage IV	Pulmonary fibrosis

- However now, *except for epidemiologic purposes* the above table classification is only of *historical interest*.
- Classically the distribution is of **bilateral (right and left) hilar and right paratracheal** nodal enlargement, which is known as the **1-2-3 sign (Pawnbroker's sign)** or **Garland triad**
- **CT of the thorax:** May demonstrate lymphadenopathy or granulomatous infiltration.
- **Whole body gallium-67 scanning: Lambda pattern** (is produced by uptake of right paratracheal and bilateral hilar lymph nodes). **"Panda image"** (produced by symmetric uptake by lacrimal and parotid glands).
- **Kveim Siltback test:** It is the **most specific** test for sarcoidosis – involves **intra-dermal injection** of tissue

from spleen or lymph node of a patient with sarcoidosis. The area is **biopsied 4–6 weeks** after injection and histologically examined for **noncaseating granuloma** formation, which, if found, means a **positive** result.

Microscopy of Sarcoidosis

- **Noncaseating granulomas; also called "naked" granulomas** since they only have a **sparse lymphocytic infiltrate** at the margins; granulomas contain inclusions like
- **Schaumann bodies** (concentric calcific concretion conch like)
- **Asteroid bodies** (stellate structures)
- **Residual bodies** (refractile calcium containing inclusions)

- **Tuberculin skin test:** Two-third patients will have **cutaneous anergy to tuberculin skin test**.
- **Bronchoalveolar lavage** with a CD4/CD8 ratio: **CD4/CD8 ratio of > 3.5** has a **94% specificity** for sarcoidosis.
- **Treatment:** DOC for sarcoidosis is **glucocorticoids**.

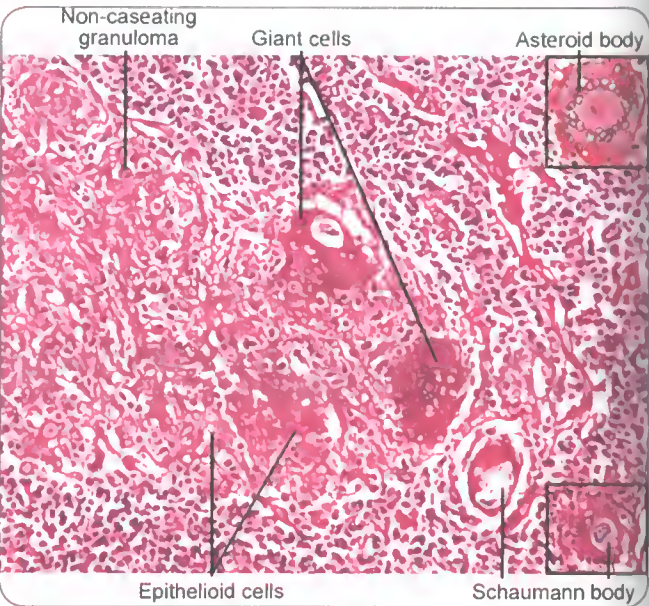


Fig. 21.61: Microscopic appearance of sarcoidosis showing noncaseating granuloma composed of epithelioid cells surrounded by lymphocytes and giant cells. Inset shows giant cell with asteroid body (upper right) and Schaumann body (lower right)

PULMONARY EMBOLISM (PE)

Risk Factors

- **Heredity** (genetic hypercoagulability)
- **History** (prior PE or DVT)
- **Hypomobility** (fracture, long travel, surgery, obesity)

- **Hypovolemia** (dehydration)
- **Hypercoagulability** (cancer, smoking)
- **Hormones** (pregnancy, OCPs) **Hyperhomocysteinemia**.

Diagnosis of Pulmonary Embolism

- **Pulmonary angiography:** still the **gold standard**.
- **CT chest with contrast: Best method** (Sixth-order branches can be visualized with resolution superior to conventional invasive contrast pulmonary angiograph; hence has virtually replaced invasive pulmonary angiography as a diagnostic test.)
- **Ventilation perfusion scan:** may demonstrate areas of V/Q mismatch, **next best to CT**.
- **ECG:** S wave in lead I, Q wave in lead III, T wave inversion in lead S1Q3T3 (not very sensitive or specific)
- **Arterial blood gases:** primary respiratory. Alkalosis and ↑ A-a gradient.
- **Chest X-ray signs - see below table**

Clinically

- **Sudden dyspnea**, pleuritic **chest pain**, **nonproductive cough**, **calf pain** and possibly **syncope**.
- **Tachypnea**, **tachycardia**, **cyanosis**, loud **S2**, **rales**; sometimes low grade fever, **hemoptysis**.

Treatment

- **Supplemental oxygen**
- **Anticoagulation:** IV heparin or LMWH; continue for 3-6 months.
- The **therapeutic window for using fibrinolytic therapy (r-TPA or streptokinase)** is **upto 14 days** although maximum benefit is usually obtained when given within 48 hours.

Chest X-ray signs in pulmonary embolism	
Embolism without Infarction (90%)	Embolism with Infarction (10%)
<ul style="list-style-type: none">• Normal chest (most common!); Plate like atelectasis; Segmental/lobar consolidation; Pleural effusion• Westermarck sign (Focal oligemia in the embolized zone)• "Knuckle" sign (abrupt tapering off of an occluded vessel distally)• Enlarged right descending pulm. Artery (Pall's sign)• Local widening of artery by impacted embolus	<ul style="list-style-type: none">• Hampton hump (A peripheral, pleural-based, wedged-shaped density above the diaphragm)• Pleural effusion• "Melting" sign (regression of consolidation from periphery to centre; appears within days to weeks)• Fleischner lines• Plate like atelectasis; Cardiomegaly/CHF; Elevated hemidiaphragm; NO air bronchogram

EXTRA EDGE

On transthoracic ECHO, **McConnell's sign** is seen (Hypokinesia of right ventricle free wall with normal motion of RV apex).

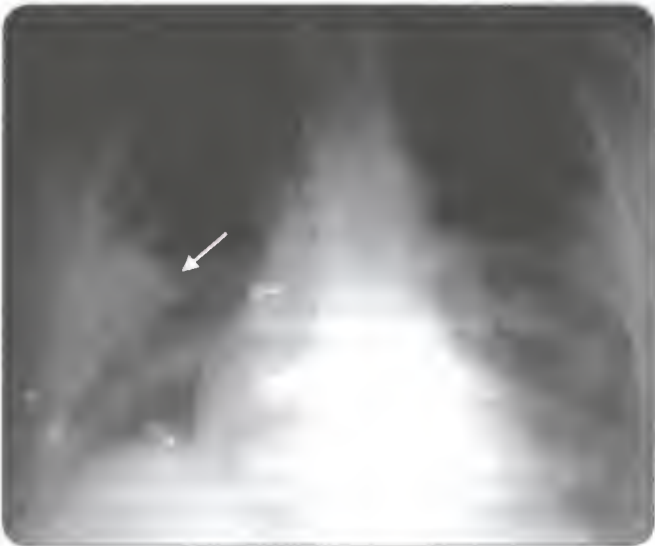


Fig. 21.62: Chest X-ray showing wedge shaped pulmonary infarct

Modified Wells Criteria for Predicting Pulmonary Embolism (PE)

- A score of <4 means PE is unlikely; >4 is suggestive of PE

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain on palpation of deep veins)	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100	1.5
Immobilisation >3 days or surgery within past 4 weeks	1.5
Previous DVT or PE	1.5
Haemoptysis	1.0
Malignancy (treatment or palliation within past 6 months)	1.0

TENSION PNEUMOTHORAX

- A **tension pneumothorax** develops when a **one-way valve air leak** occurs either from the lung or through the chest wall.

- Air is sucked into the thoracic cavity without any means of escape, completely collapsing and compressing the affected lung.
- The **mediastinum is displaced to the opposite side**, decreasing venous return and **compressing the opposite lung**.
- Patient is panicky with **tachypnea, dyspnea and distended neck veins**; **tracheal deviation** may be seen; **hyper-resonance and absent breath sounds over the affected hemithorax**.
- Treat with **immediate decompression by rapidly inserting a large bore needle into the second intercostal space** in the midclavicular line of the affected hemithorax followed by **insertion of chest tube in the fifth intercostal space in mid axillary line**.

LUNG TRANSPLANTATION

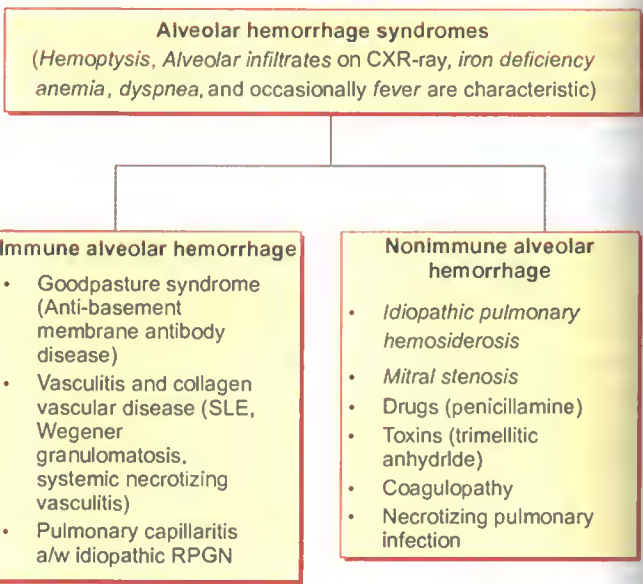
- **Father of lung transplantation:** Joel Cooper
- **MC indication in adults = COPD; in children = cystic fibrosis.**
- **Indications:**
 - COPD
 - Primary pulmonary hypertension
 - Cystic fibrosis
 - Idiopathic pulmonary fibrosis with estimated survival of < 2 years Poor cardiac function
- **Contraindications:**
 - Renal/hepatic insufficiency
 - Smokers
 - Age > 60 years.

DIAGNOSTIC CRITERIA FOR ARDS

Oxygenation	Onset
$PaO_2/FiO_2 \leq 200$ mmHg	Acute
Chest X-ray	Absence of left atrial HTN
Bilateral alveolar or interstitial infiltrates	PCWP ≤ 18 mmHg or no clinical evidence of increased left atrial pressure

EXTRA EDGE

- **Mortality in ARDS** is largely attributable to **non-pulmonary causes**, with **sepsis and non-pulmonary organ failure accounting for > 80% of deaths**.
- ARDS is a life-threatening complication of talc pleurodesis.



EXTRA EDGE

- **Rapid clearing** of diffuse lung infiltrates **within 2 days** is a clue to the diagnosis of diffuse alveolar hemorrhage.

RESPIRATORY FAILURE

Hypoxemic respiratory failure	Hypercarbic respiratory failure
<ul style="list-style-type: none">• MC due to conditions that cause ventilation-perfusion (V/Q) mismatch and shunt:<ul style="list-style-type: none">- Pneumonia, Pulmonary edema, Pulmonary hemorrhage, and Respiratory distress syndrome.• $PaO_2 < 60$ mmHg (< 8 kPa) and $PaCO_2$ is either low or normal• Clinically: dyspnea, confusion, tachypnea, tachycardia, arrhythmias	<ul style="list-style-type: none">• Due to conditions that decrease minute ventilation or increase physiologic dead space such that alveolar ventilation is inadequate to meet metabolic demands:<ul style="list-style-type: none">- Neuromuscular diseases - myasthenia gravis, ascending polyradiculopathy, and myopathies- Diseases that cause respiratory muscle fatigue due to increased workload, such as asthma, chronic obstructive pulmonary disease, and restrictive lung disease.• $PaO_2 < 60$ mmHg (< 8 kPa) and $PaCO_2$ is high (> 50 mmHg or > 6 kPa) and an arterial pH < 7.30.• Clinically: dyspnea, headache, hypertension, tachycardia, tachypnea, papilledema, asterixis.

OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME (OSAHS)

- Recurrent episodes of **airway collapse during sleep** → patient stops breathing for at least **10 seconds** → **intermittent hypoxia** and **recurrent arousals**.
- A/w
 - Obesity, Males, Systemic/pulmonary hypertension
 - Large neck circumference
 - Mandibular retrognathia and micrognathia,
 - A positive family h/o OSAHS,
 - Genetic syndromes that reduce upper airway patency (e.g., Down syndrome, Treacher-Collins syndrome),
 - Adenotonsillar hypertrophy (especially in children),
 - Menopause (in women),
 - Endocrine syndromes (e.g. acromegaly, hypothyroidism).
- **Clinically:** Morning headache, loud snoring, unrefreshing sleep, daytime sleepiness; chronic tiredness, arrhythmias and sudden death.
- **Diagnosis:**
 - **Gold standard** is **overnight polysomnography (sleep study)**.
 - **Five or more** episodes of apnea or hypopnea per hour of sleep, i.e. the Apnea/Hypopnea index (**AHI**) > 5 is **diagnostic of OSA**. (AHI 5-14 is mild; 15-29 is moderate and >30 is severe OSAHS)
 - **STOP - BANG** questionnaire is used.
 - **Muller's maneuver** is performed with flexible nasopharyngo-laryngoscopy to find the level and degree of obstruction in OSA.
- Treatment
 - Encourage **weight loss**; optimize sleep duration; avoid sleeping in supine position; avoid alcohol within 3 hours of bedtime.
 - **CPAP** (continuous positive airway pressure) is **most effective treatment** - A type of **non-invasive ventilation**.
 - Surgery (**uvulo-palato-pharyngo-plasty**, UPPP) is effective in only 40-50% cases.

Note

- Diagnosis of **Obesity Hypoventilation Syndrome (Pickwickian syndrome)** requires: body mass index (**BMI**) >30kg/m², **sleep-disordered breathing** (severe sleep apnea), **chronic daytime alveolar hypoventilation** ($PaCO_2 > 45$ mmHg) and hypoxia ($PaO_2 < 70$ mmHg)

CAISSON'S DISEASE

- Also called **hyperbaric decompression sickness, the 'bends, diver's palsy**.
- A specialized form of **gas embolism**.
- In divers who descend to high atmospheric pressures underwater, increased amounts of atmospheric gases (mainly nitrogen) are dissolved in blood and tissue fluids.
- When such a person **ascends too rapidly, nitrogen** comes out of solution as minute bubbles, particularly in fatty tissues which have high affinity for nitrogen. These bubbles may coalesce together to form large emboli.
- **Bends:** Acute pain in joints, ligaments and tendons
- **Chokes:** Respiratory distress.
- Treatment is **immediate hyperbaric oxygen therapy**.

NONSPECIFIC INTERSTITIAL PNEUMONIA

- MC in young women; nonsmokers;
- HRCT shows bilateral subpleural ground glass opacities with lower lobe volume loss:
 - NO honeycombing;
 - a/w good prognosis

COMMON DRUGS CAUSING INTERSTITIAL PNEUMONITIS/PULMONARY FIBROSIS

- Bleomycin
- Busulfan
- Amiodarone
- Methotrexate
- Cyclophosphamide
- Nitrosureas
- Nitrofurantoin
- Sulfonamides
- Gold salts
- Penicillamine
- Phenytoin
- Methysergide

LIVER

Liver Enzymes

- Enzymes that reflect damage to Hepatocytes:
 - The *aminotransferases (transaminases)*—include *aspartate aminotransferase (AST)* and *alanine aminotransferase (ALT)*.
 - AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration.
 - ALT is found **primarily in the liver** and is therefore a **more specific indicator** of liver injury.
- Enzymes that reflect Cholestasis
 - Alkaline phosphatase
 - 5'-nucleotidase
 - γ -glutamyl transpeptidase (GGT)
 - Lipoprotein-X** is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice and thus is a **sensitive indicator of cholestasis**.

Causes of Fatty Liver

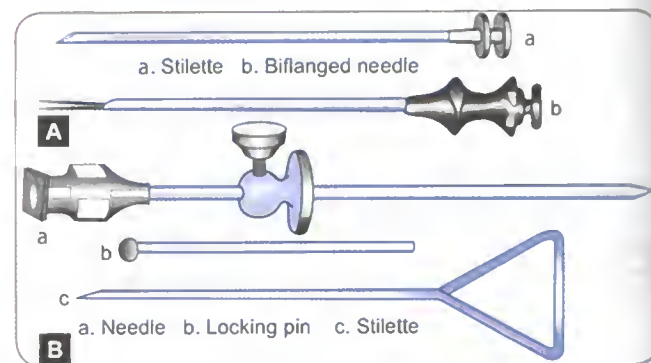
Macrovesicular (large fat droplets in hepatocytes)	Microvesicular (small fat droplets in hepatocytes)
<ul style="list-style-type: none"> Alcoholic liver disease Protein-calorie malnutrition Diabetes mellitus Obesity Total parenteral nutrition, jejunoileal bypass Drugs: aspirin, amiodarone, vitamin A, glucocorticoids, methotrexate, synthetic estrogen, zalcitabine 	<ul style="list-style-type: none"> Reye's syndrome Acute fatty liver of pregnancy Jamaican vomiting sickness Drugs: Tetracycline, Valproic acid, Didanosine, Stavudine, Zidovudine "RAJ TV DSZ (disease)!"

Drug Induced Liver Injury

- Direct toxic injury:**
 - Carbon tetrachloride** (necrosis, fatty infiltration)
 - Acetaminophen** (centrilobular necrosis)
- Idiosyncratic reaction:**
 - Amoxicillin-clavulanate (Mixed hepatocellular/cholestatic)
 - Isoniazid and ciprofloxacin (Hepatocellular injury resembling viral hepatitis)
- Estrogens/Androgenic steroids (cholestatic without portal inflammation).

Important Diagnostic Tests in Common Liver Diseases

Disease	Diagnostic test
Autoimmune hepatitis	ANA (Antinuclear Antibody); SMA (Smooth Muscle Antibody), Anti-LKM antibody (see more below) elevated IgG levels and compatible histology
Anti-LKM 1 antibody	Autoimmune hepatitis type 2 Chronic Hepatitis C Halothane induced hepatitis, Graft versus host reaction
Anti-LKM 2 antibody	Drug induced hepatitis Tienilic acid induced hepatitis
Anti-LKM 3	Chronic hepatitis D
Hemochromatosis	Elevated iron saturation and serum ferritin, genetic testing for HFE gene mutations
Wilson's disease	Decreased serum ceruloplasmin and increased urinary copper; increased hepatic copper level
Alcoholic liver disease	History of excessive alcohol intake and compatible histology
Non alcoholic steatohepatitis	U/S or CT evidence of fatty liver and compatible histology
α -1 Antitrypsin disease	Reduced α -1 antitrypsin levels, phenotypes PiZZ or PiSZ
Hepatocellular cancer	Elevated α -fetoprotein level > 500; ultrasound or CT image of mass
Primary biliary cirrhosis	Anti-mitochondrial antibody (AMA), IgM levels, and compatible histology
Primary sclerosing cholangitis	p-ANCA, cholangiography



Figs. 21.63A and B: Liver biopsy needles. A. Vim-Silvermann, B. Menghini

CIRRHOSIS

Alcoholic Cirrhosis

- Liver and spleen may be enlarged, with the liver edge being firm and nodular.
- Other findings include **scleral icterus, palmar erythema, spider angiomas, parotid gland enlargement, digital clubbing, muscle wasting**, or the development of **edema and ascites**.
- Men may have decreased body hair and **gynecomastia** as well as **testicular atrophy**.

PORTAL HYPERTENSION

Variceal Bleeding

- Varices usually present with the acute onset of a large-volume **hematemesis, the lower oesophagus** being the **MC site** for variceal bleeding.
- Management** of bleeding oesophageal varices:
 - Blood transfusion
 - Correct coagulopathy
 - Oesophageal balloon tamponade (*Sengstaken-Blakemore*)
 - Tube
 - Drug therapy (vasopressin/octreotide)
 - Endoscopic sclerotherapy or banding
 - Assess portal vein patency (Doppler ultrasound or CT)
 - Transjugular intrahepatic portosystemic stent shunts (**TIPSS**)
 - Surgery (Portosystemic shunts; Oesophageal transection; Splenectomy and gastric devascularization).

Ascites

- Ascites is the accumulation of fluid within the peritoneal cavity.
- MC cause** of ascites is **portal hypertension** related to cirrhosis.
- Increase in abdominal girth a/w development of peripheral edema, abdominal discomfort and a dragging sensation.
- Imaging by **CT will confirm the ascites** and demonstrate the **irregular and shrunken nature of a cirrhotic liver** and **associated splenomegaly**.
- Treatment of ascites** in chronic liver disease:
 - Salt restriction
 - Diuretics
 - Abdominal paracentesis
 - Peritoneovenous shunting — from *peritoneum* to *superior vena cava* (**Leveen shunt**)
 - Transjugular intrahepatic portosystemic stent shunts (**TIPSS**)
 - Liver transplantation.

SAAG

- Serum-ascites albumin gradient (SAAG)** is more useful than the total protein concentration of ascitic fluid in the classification of ascites.
- This gradient is physiologically based on oncotic hydrostatic balance and is related directly to portal pressure.
- SAAG is calculated by** subtracting albumin concentration of ascitic fluid from albumin concentration of serum obtained on the same day.
- SAAG** = serum albumin – ascitic fluid albumin.

SAAG ≥ 1.1 gm/dL

- Cirrhosis** (MC cause) leading to **Portal HTN**
- Portal HTN from any cause (alcoholic hepatitis, cardiac ascites, massive liver metastasis, fulminant hepatic failure, Budd Chiari syndrome, portal vein thrombosis, veno occlusive disease, myxema, fatty liver of pregnancy, mixed ascites)

SAAG ≤ 1.1 gm/dL

- Normal portal pressure
- Peritoneal disease** (peritoneal carcinomatosis – MC cause)
- Others – TB peritonitis, pancreatic disease, biliary ascites, nephrotic syndrome, serositis and bowel obstruction or infarction)

Hepatic Encephalopathy

- A.k.a '**portosystemic encephalopathy**'.
- Defined as "an alteration in mental status and cognitive function occurring in the presence of liver failure".
- Gut-derived neurotoxins** that are not removed by the liver because of vascular shunting and decreased hepatic mass get to the brain and cause the below symptoms.
- Clinically:** Drowsiness, confusion, disorientation, unconsciousness; asterixis, constructional apraxia, **feter hepaticus**.
- Labs: $\uparrow\uparrow$ **Ammonia levels**; EEG shows **diffuse slowing of normal alpha waves** with eventual development of delta waves.
- Treatment:
 - Lactulose (mainstay of treatment)**, a **nonabsorbable disaccharide**, which results in colonic acidification and catharsis ensues, leading to the elimination of nitrogenous products in the gut.
 - Lactitol** is a palatable alternative.
 - Poorly absorbed antibiotics may be used for the same purpose - alternating administration of **neomycin** and **metronidazole** (recently **rifaximin**).
 - Zinc supplementation** is sometimes helpful.
 - Dietary protein restriction** is rarely needed and **NO longer recommended**.

CLASSIFICATION OF PORTAL HYPERTENSION

Prehepatic	Intrahepatic (IH)	Extrahepatic (EH)
<ul style="list-style-type: none">• Portal vein thrombosis• Splenic vein thrombosis• Massive splenomegaly (Banti's syn.)	<ul style="list-style-type: none">• IH Presinusoidal<ul style="list-style-type: none">- Schistosomiasis- Congenital hepatic fibrosis- Sarcoidosis- Vinyl chloride- Drugs• IH Sinusoidal<ul style="list-style-type: none">- Cirrhosis (MC)- Cystic liver disease- Partial nodular transformation of liver- Metastatic malignant disease- Alcoholic hepatitis• IH Postsinusoidal<ul style="list-style-type: none">- Hepatic sinusoidal obstruction (venoocclusive syndrome)	<ul style="list-style-type: none">• EH Postsinusoidal (posthepatic)<ul style="list-style-type: none">- Budd-Chiari syndrome- Inferior vena caval webs- Cardiac causes- Restrictive cardiomyopathy- Constrictive pericarditis- Severe congestive heart failure• EH Presinusoidal<ul style="list-style-type: none">- Portal vein thrombosis due to sepsis (umbilical, portal pyemia) or procoagulopathy (thrombotic diseases, OCPs, pregnancy), or secondary to cirrhosis.- Abdominal trauma including surgery- Malignant disease of pancreas or liver- Pancreatitis- Congenital

BUDD-CHIARI SYNDROME

- Thrombosis of **larger hepatic veins** and sometimes **inferior vena cava** (IVC)
- Sudden venous occlusion = Acute upper abdominal pain, **marked ascites**.
- Gradual venous occlusion = **Gross ascites**, tender hepatomegaly
- Complications: Peripheral edema (IVC obstruction), cirrhosis, portal hypertension
- U/S with Doppler imaging may reveal obstruction and is the first test done in suspects.
- Treat with streptokinase, oral anticoagulants, TIPSS
- Prognosis without liver transplantation or shunting is poor
- **Budd-Chiari syndrome** is a cause of **extrahepatic post-sinusoidal** portal hypertension.

Reye's Syndrome

- Rare, often **fatal childhood** hepatoencephalopathy due to viral infection (esp. vzv or influenza b) that has been treated with **aspirin** (salicylates); maybe due to **impaired beta-oxidation** of fatty acids.
- Features: Hypoglycemia, coma, fatty liver (**microvesicular**).
- Do not use aspirin in children.

WILSON'S DISEASE

Etiology

- A.k.a (**Hepatolenticular Degeneration**)
- **AR**, inherited disorder of copper homeostasis; a/w **mutation in ATP7B gene** → results in **excess**

accumulation of copper in **liver** and **brain** (basal ganglia), **cornea**, kidneys and joints.

Diagnosis

- **Leipzig** scoring for **predicting diagnosis of Wilson's disease** includes:
 - **Serum ceruloplasmin**, which is **typically decreased by 50%** of the lower normal value (ceruloplasmin is an alpha 2 globulin)
 - **24-hours urinary copper excretion**, which is **typically > 100 mcg/24 h** in adults
 - **Serum free copper**, which is **typically > 200 mcg/L**
 - **Hepatic copper**, which is **typically > 250 mcg/g dry weight**
 - Presence of **Kayser-Fleischer rings** on slit-lamp examination (may be absent in up to 50% of patients with hepatic WD)
- If score is **4 or more**: Diagnosis established; if **score is 3**: Diagnosis possible, more tests needed; if **score is 2 or less**: Diagnosis very unlikely
- **Liver biopsy** is the **GOLD** standard test.

Treatment

- **Restriction of dietary copper** (shell sh, organ foods, nuts, mushrooms, and chocolate)
- **Copper chelating** agents (**Trientine** recommended > Penicillamine).
- **Oral zinc** acetate competes with copper absorption in the gut and induces metallothionein in the intestine, which then sequesters copper and **promotes fecal copper excretion**.
- **Oral Zinc** is the **first choice drug** for initial hepatitis without decompensation; for **pediatric and pregnant**

patients; for pre-symptomatic patients and for **maintenance**.

EXTRA EDGE

- Wilson's disease **severity** can be established with **Nazer prognostic index** (measures serum bilirubin, serum aspartate aminotransferase; prolongation of prothrombin time)

Clinical features of Wilson's Disease

- **Liver related features**: **Chronic hepatitis, hepatic steatosis, and cirrhosis** in **adolescents and young adults**.
- **CNS features**: indicates that liver disease is present and include **speech disorders** and various **movement disorders** (wing beating tremors).
- **Eye**: **Kayser-Fleischer rings** in the periphery of cornea – **copper deposition in Descemet's membrane**; best seen by **slit lamp examination**.

HEMOCHROMATOSIS

- **Bronze diabetes** = Triad of: Hemochromatosis, Micronodular cirrhosis, Diabetes mellitus.
- **Hemosiderosis** is the deposition of iron; when total body **iron is higher than 25-30 gm**, hemosiderosis is manifested.

RENAL SYSTEM

ACUTE KIDNEY INJURY (AKI)

- **Acute kidney injury**, earlier known as **acute renal failure**, is **abrupt worsening** of kidney function over **hours to days** with a **reduction in urine output**, resulting in the **retention of nitrogenous wastes** (such as **urea nitrogen** and **creatinine**) in the blood.
- Retention of these substances is called **azotemia**.
- **Oliguria** (< **300 cc/day**) is not a must for ARF but should prompt one to look for it.
- **RIFLE criteria**: describe three progressive levels of acute kidney injury (Risk, Injury, and Failure) based on

the elevation in serum creatinine or decline in urinary output with two outcome measures (loss and ESRD):

- Risk = 1.5-fold increase in serum creatinine
- Injury, = a twofold or threefold increase in serum creatinine
- Failure = decline in urinary output to 0.5 mL/kg/h over 6, 12, or 24 hours.
- **AKIN criteria**: closely follow the RIFLE criteria, with the addition of a **change in serum creatinine of 0.3 mg/day** qualifying as a risk for injury.
- Causes of Acute Renal Failure (ARF) are:

Prerenal azotemia	Intrinsic AKI	Postrenal AKI
<p>↓ Renal blood flow → ↓ GFR, Na⁺/H₂O and urea retained by the kidney.</p> <p>MC type of AKI</p> <p>Occurs due to:</p> <ul style="list-style-type: none">• Dehydration (anorexia, burns, GI losses)• ACEIs/ARBs, NSAIDs, cyclosporine• Shock (cardiogenic - decreased cardiac output, hypovolemic - blood loss)• Hepatorenal syndrome (congestive heart failure, liver failure)• Cardiomyopathies	<p>Patchy necrosis leads to debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR, urine has epithelial/granular casts</p> <p>Occurs due to:</p> <ul style="list-style-type: none">• Glomerular - Acute glomerulonephritis• Vascular: Vasculitis, TTP-HUS, malignant HTN, eclampsia• Ischemia of tubules - Acute tubular necrosis• Exogenous nephrotoxins: Drugs (aminoglycosides, cisplatin, amphotericin-B); poisons; contrast media• Endogenous nephrotoxins: hemolysis, rhabdomyolysis, Myoglobinuria, myeloma, DIC	<p>Bilateral outflow obstruction</p> <p>Occurs due to:</p> <ul style="list-style-type: none">• Ureteral (stones, papillary necrosis, stenosis)• BPH; prostatic neoplasia• Bladder outlet obstruction

Differences between Prerenal and Intrinsic Renal Azotemia

Diagnostic indices	Prerenal (hypovolemia)	Intrinsic (ATN)
Urine osmolality	> 500	< 350
BUN/Cr ratio	> 20	< 15
Urine Na	< 10	> 20
Fe _{Na}	< 1%	> 2%

Urinary Casts in AKI

Type	Significance
RBC casts	Glomerulonephritis
WBC casts	(indicative of infection or inflammation) – pyelonephritis, interstitial nephritis
Broad waxy casts	(indicative of stasis in collecting tubule) – chronic renal failure
Renal tubular cell casts	Acute tubular necrosis, interstitial nephritis
Glomerular ‘muddy brown’ casts	Acute Tubular Necrosis (ATN)
Hyaline casts	Nonspecific, maybe normal finding or indicative of – concentrated urine, febrile diseases, after strenuous exercise, in the course of diuretic therapy
Coarse, granular casts	Nonspecific, can represent acute tubular necrosis
RBCs	Indicates hematuria; absence of RBCs when the dipstick is positive for blood suggests hemoglobinuria from hemolysis or myoglobinuria from rhabdomyolysis
WBCs	Infection, acute cystitis, nephrolithiasis

Biomarkers of Acute Kidney Injury

- ▶ Alanine aminopeptidase (AAP)
- ▶ Alkaline phosphatase (AP)
- ▶ α-Glutathione-S-transferase (- GST)
- ▶ γ-Glutamyl transpeptidase (GT)
- ▶ N-Acetyl- -(D) glucosaminidase (NAG)
- ▶ β2-Microglobulin
- ▶ α1-Microglobulin
- ▶ Retinol-binding protein
- ▶ Cystatin C
- ▶ Microalbumin
- ▶ Kidney injury molecule-1 (KIM- 1)
- ▶ Clusterin
- ▶ Neutrophil elatinate associated lipocalin (NGAL)
- ▶ Interleukin-18 (IL- 18).
- ▶ Cysteine-rich protein (CYR-61)
- ▶ Osteopontin
- ▶ Liver fatty acid –binding protein (L-FABP)
- ▶ Sodium/hydrogen exchanger isoform (NHE3)
- ▶ Exosomal fetuin-A.

CHRONIC KIDNEY DISEASE

- Chronic kidney disease (CKD) is a/w abnormal kidney function and a progressive decline in GFR.
- *Kidney Disease Improving Global Outcome (KDIGO)* classification of chronic kidney disease: Stages of CKD are stratified by both estimated **GFR** and the *degree of albuminuria*, in order to predict risk of progression of CKD.
- The term **end-stage renal disease (ESRD)** represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the **uremic syndrome**.
- **ESRD** corresponds to **stage 5 CKD**.

Etiologies of CKD

- Diabetic nephropathy (MC cause)
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy.

Consequences of CKD/Uremia

- CKD results in failure of kidneys to make urine and excrete nitrogenous wastes and to maintain fluid and electrolyte balance.
- **Uremia** is a clinical syndrome marked by ↑ BUN and ↑ creatinine and associated symptoms.
- Consequences are:
 - ▶ **Anemia** (failure of erythropoietin production)
 - ▶ **Renal osteodystrophy** (failure of active vitamin D production); Patients with **GFR <60 mL/min/1.73 m²** should be **evaluated for bone disease**.
 - ▶ **Hyperkalemia** which can lead to cardiac arrhythmias
 - ▶ **Metabolic acidosis** due to ↓ acid secretion and ↓ generation of HCO₃⁻
 - ▶ Uremic **encephalopathy**
 - ▶ Na⁺ and H₂O excess – **CHF and pulmonary edema**
 - ▶ Chronic **pyelonephritis**
 - ▶ **Hypertension**.

Indications for Emergency Dialysis in Renal Failure

- Acidosis
- Electrolytes
- Ingestion (of toxins)
- Overload (volume)
- Uremic symptoms (encephalopathy, pericarditis) (“**AEIOU!**”).

Treatment of CKD

- **Dialysis** may be required for the treatment of either acute or chronic kidney disease.
- Estimated glomerular filtration rate (GFR) below 10 mL/min per 1.73 m² is an indication for dialysis.
- Types of dialysis include:
 - ▶ **Hemodialysis** (MC therapeutic modality for ESRD, >90% patients)
 - ▶ **Peritoneal** dialysis, as either continuous ambulatory peritoneal dialysis (**CAPD**) or continuous cyclic peritoneal dialysis (**CCPD**).

Complications of hemodialysis

- ▶ Hypotension
- ▶ Hemorrhage
- ▶ Muscle cramps
- ▶ Hyperkalemia
- ▶ Leukopenia
- ▶ Arrhythmias
- ▶ Sepsis
- ▶ Pyrogenic reactions
- ▶ Dialysis disequilibrium syndrome
- ▶ Hypoxemia
- ▶ Angioaccess dysfunction
- ▶ Air embolism
- ▶ Anaphylactoid reaction to the dialyzer.

Calciophylaxis

- Calcific uremic arteriolopathy (calciophylaxis) is a devastating condition seen almost exclusively in patients with advanced CKD.
- It is heralded by **livedo reticularis** and advances to **patches of ischemic necrosis**, especially on the legs, thighs, abdomen, and breasts.

Type	Pathology	Clinical features, treatment and remarks
Minimal change disease, lipoid nephrosis	<ul style="list-style-type: none">LM – Normal (hence ‘nil’ disease)IF – negativeEM – fusion and effacement of epithelial foot processes (podocytes)	<ul style="list-style-type: none">MC cause of childhood nephrotic syndromeTreat with corticosteroidsRelapse possible but most patients have good prognosis with eventual cessation of relapses
Membranous glomerulonephritis	<ul style="list-style-type: none">LM – diffuse capillary and GBM thickeningIF – negativeEM – “spike and dome” basement membrane thickening	<ul style="list-style-type: none">MC nephropathy a/w malignancyA/w: lymphoma, Malaria, HBV, Syphilis and Drugs (gold, penicillamine, captopril)Treat with corticosteroids
Focal segmental glomerulosclerosis	<ul style="list-style-type: none">5 types are seen on renal biopsy:▶ Collapsing type - a/w HIV and worst prognosis; also a/w pamidronate; proliferation and hypertrophy of glomerular visceral epithelial cells seen▶ Glomerular tip lesion variant;▶ Cellular variant▶ Perihilar variant;▶ NOS (not otherwise specified) - MC subtype▶ LM – segmental sclerosis and hyalinosis	<ul style="list-style-type: none">A/w HIV, IV drug abuse/heroin use, idiopathicMC cause of adult nephrotic syndrome

- Risk factors include **hyperparathyroidism** in dialysis patients and **warfarin therapy**.

Renal Transplantation

- Transplantation of the human kidney is the **treatment of choice for advanced chronic renal failure**.
- Mortality rates after transplantation are **highest in the first year**.
- The transplant procedure is relatively noninvasive, as the organ is placed **in the inguinal fossa** without entering the peritoneal cavity.
- Immunosuppressive treatment following renal transplantation includes: **glucocorticoids, cyclosporine, tacrolimus azathioprine, mycophenolate mofetil, sirolimus/everolimus** and **belatacept** (Binds CD80 and CD86, prevents CD28 binding and T-cell activation).

Most Common Opportunistic Infections in Renal Transplant Recipients

- Peritransplant: Wound infections; Herpesvirus; Oral candidiasis; Urinary tract infection.
- Early (1–6 months): Pneumocystis jiroveci; CMV; Legionella; Listeria; HBV, HCV.
- Late (>6 months): **Aspergillus; Nocardia; BK virus (polyoma)**; Herpes zoster; HBV, HCV.

NEPHROTIC SYNDROMES

- Massive **proteinuria**, > 3.5 g/day (frothy urine)
- **Hypoalbuminemia**
- Peripheral and periorbital **edema, anasarca**
- **Hyperlipidemia**
- Hypertension
- Microscopic hematuria.

Type	Pathology	Clinical features, treatment and remarks
Diabetic nephropathy	<ul style="list-style-type: none">LM – Kimmelstien Wilson nodular glomerulosclerosis, BM thickening, ↑ mesangial matrix	<ul style="list-style-type: none">Generally have longstanding poorly controlled DMTight blood sugar control; ACEIsESRF occurs in 50% of patients with DM type 1 and 10% of patients with DM type 2 within 10 years of the diagnosis of the nephropathy
SLE (Lupus nephritis)	<ul style="list-style-type: none">Class I: <i>Minimal Mesangial</i>Class II: <i>Mesangial proliferative</i>Class III: <i>Focal proliferative</i>Class IV: Diffuse proliferative (wire-loop lesion with subepithelial deposits)Class V: <i>Membranous</i>Class VI: <i>Sclerosing</i>	<ul style="list-style-type: none">Positive ANA and Anti-DNA antibodiesTreat with prednisolone and cytotoxicACEIs and statins help reduce proteinuriaPrognosis correlates with severity of systemic disease
Amyloidosis	<ul style="list-style-type: none">IF – Congo red stain, apple-green birefringence on polarized microscopy	<ul style="list-style-type: none">A/w multiple myeloma, chronic conditions, TB, rheumatoid arthritis

NEPHRITIC SYNDROMES

- Hematuria with RBC casts (smoky urine)
- Hypertension
- Oliguria
- Azotemia (Rise in serum creatinine associated with a reduction in GFR)
- Proteinuria (1-2 g/24 h)
- Pyuria

Type	Pathology	Clinical features, treatment and remarks
Acute Post-streptococcal GN	<ul style="list-style-type: none">LM – glomeruli enlarged and hypercellular with neutrophils, 'lumpy-bumpy'IF – granular 'starry sky' patternEM – subepithelial deposits of IgG and C3Antigen responsible is a cytoplasmic antigen called endostreptosin and a cationic proteinase antigen called nephritis strain associated protein (NSAP)	<ul style="list-style-type: none">Occurs 2 weeks after streptococcal pharyngitis/pyodermaLow C3; Normal C4;High ASD titerSelf limited; supportive treatment (decrease edema and hypertension).Prognosis excellent in children
Rapidly Progressive GN (Crescentic GN), RPGN	<ul style="list-style-type: none">Type 1 RPGN - anti GBM antibody (Goodpasture syndrome)Type 2 RPGN - Immune complex (postinfectious, SLE, HSP)Type 3 RPGN - Pauci-immune type (a/w Polyarteritis nodosa, Wegener's, Positive ANCA, NO Ig deposits)Inflammatory cell deposition in Bowman capsule and crescent formation (crescents are composed of parietal cells, leucocytes and macrophages)	<ul style="list-style-type: none">Rapid course to renal failure due to idiopathic cause, other glomerular diseases or systemic infection.Corticosteroids, plasmapheresis and immunosuppressive agents maybe helpful to slow progression. Renal transplant is frequently requiredNumber of crescents indicates prognosis
Membranoproliferative (mesangiolproliferative) GN	<ul style="list-style-type: none">Primary/Idiopathic MPGN has 2 types.Type 1 - MC; MPGN; on EM has subendothelial humps, basement membrane thickening with double layer 'tram-track'Type 2 MPGN is dense deposit disease; intramembranous deposits	<ul style="list-style-type: none">A/w HCV, infections, autoimmune, idiopathicAll types have Low C3, Type II involves C1 nephritic factor50% present as nephrotic syndrome. Slowly progresses to renal failure > 10 yearsCorticosteroids in children, Aspirin or dipyridamole useful in adults
Goodpasture's syndrome (pulmonary-renal synd.)	<ul style="list-style-type: none">IF – linear pattern of anti GBM antibodiesA type of type 1 RPGN	<ul style="list-style-type: none">Hemoptysis, chest pain, dyspnea, hematuriaType II hypersensitivityTreat with plasmapheresis

Contd...

Type	Pathology	Clinical features, treatment and remarks
IgA Nephropathy (Berger's disease)	<ul style="list-style-type: none">Mesangial IgA deposits; CD71 mesangial IgA1 receptor is expressed more	<ul style="list-style-type: none">Painless, recurrent hematuria in young men usually Asian origin; 24-48 hours after pharyngeal/GI infectionSimilar picture seen in HSP; good prognosis in children; Omega-3 fatty acids used for Rx.

Key: LM = light microscopy; IF = immunofluorescence; EM = electron microscopy; GBM = glomerular basement membrane; CRF = chronic renal failure; HSP = Henoch-Schonlein Purpura



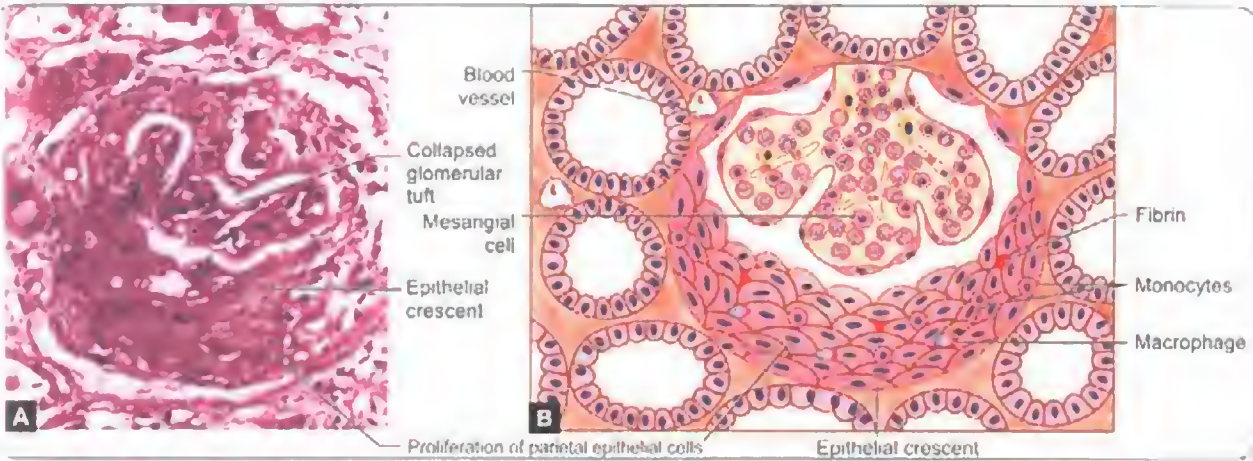
Fig. 21.64: Granular immunofluorescence characteristic of circulating or in situ immune complex nephritis



Fig. 21.65: Linear immunofluorescence for immunoglobulin G is seen along the GBM in Goodpasture syndrome

EXTRA EDGE

- The classical pathologic manifestation of parietal epithelial cell injury is **crescent formation**.
- **Alports'** syndrome is the MC hereditary nephritis and is X-linked dominant, Anterior **Lenticonus**, sensorineural deafness. **"Basket weave"** appearance on **electron microscopy** is **diagnostic**; a/w **COL4A5** (alpha 5 chain of Collagen type IV) mutation.
- **Thin basement membrane disease**: it is a **variant of Alport's syndrome**; thin basement membranes are found in 5%–10% of the so-called normal population. These subclinical patients have **normal blood pressure** and **little proteinuria** and they **rarely** progress to renal failure
- **Renal biopsy** is the **gold standard** for diagnosis of glomerulonephritis.
- Proteinuria of nephrotic syndrome is typically **nonselective in adults**.



figs. 21.66A and B: A. (H and E stain) and B. Diagrammatic representation of crescentic glomerulonephritis showing crescent shaped mass of proliferating parietal epithelial cells and leukocytes internal to Bowman capsule

Contd

MORPHOLOGICAL KIDNEY APPEARANCES

Large Kidney

- Diabetic nephropathy
- Amyloidosis
- Scleroderma
- Polycystic disease
- Medullary cystic/sponge kidney
- Acute glomerulonephritis.

Small Contracted Kidney

- Chronic GN
- Chronic Pyelonephritis
- Benign Nephrosclerosis.

Flea Bitten Kidney

- Petechial hemorrhages on the renal surface grossly looks like fleas have bitten the entire kidney:
- Malignant hypertension
 - (HSP) Henoch-Schönlein Purpura
 - (SABE) Subacute Bacterial Endocarditis
 - (APGN) Acute Post Streptococcal Glomerulonephritis
 - (RPGN) Rapidly Progressive GN
 - (HUS) Hemolytic Uremic Syndrome
 - (TTP) Thrombotic Thrombocytopenic Purpura
 - Leukemia, lymphoma, myeloma.

DIABETIC NEPHROPATHY

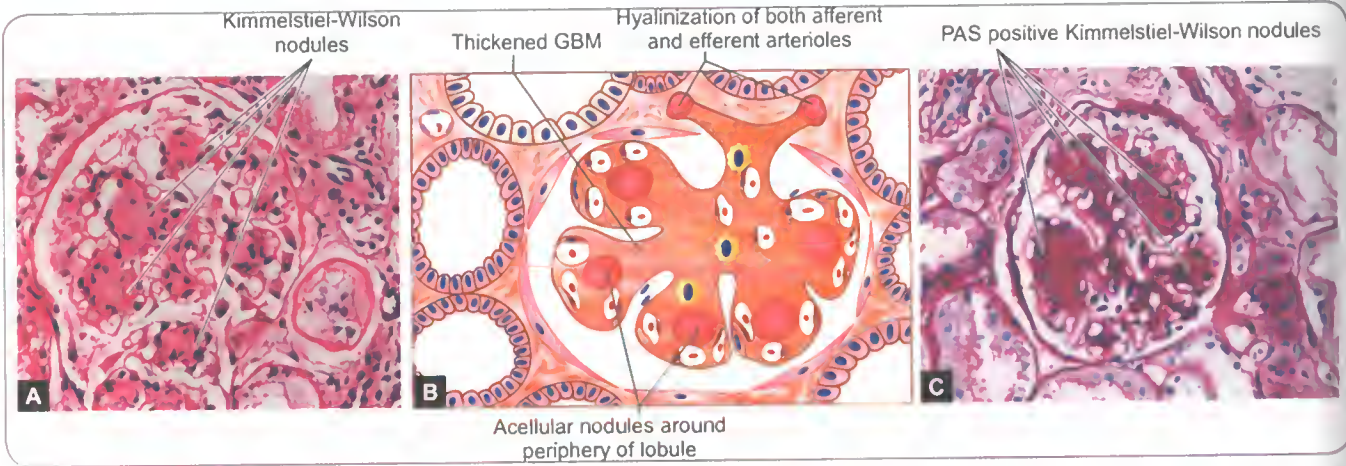
The *first/earliest stage of diabetic nephropathy is hyperfiltration, with an increase in GFR, followed by the development of microalbuminuria (usually 5–10n years later).*

- *Microalbuminuria* = 30–300 mg/24 h.
- *Macroalbuminuria* = > 300 mg/24 h.
- *Screening for microalbuminuria: Yearly* from the time of diagnosis in ALL diabetics.
- Diabetic nephropathy is *a/w Diabetic retinopathy* (60% in type 2 and 90% in type 1). Thus don't forget to screen for retinopathy in DM!
- The **MC lesion** in diabetic nephropathy is *diffuse glomerulosclerosis*, but *nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)* is *pathognomonic*.
- ACE inhibitors and ARBs lower the rate of progression to clinical proteinuria and slow progression to ESRD by reducing intraglomerular pressure as well as by treating hypertension; they may also have antifibrotic effects.
- *Diabetic nephropathy* is the **MC cause of chronic renal failure and end stage renal disease** requiring renal replacement therapy.
- In *uncontrolled diabetes* there is glucosuria resulting in glycogen accumulation in proximal tubular cells (*Armanni Ebstein cells*).

MORE RENAL TOPICS

Basement Membrane Syndrome

- Patients either have genetically abnormal basement membranes or an *autoimmune response to basement membrane collagen IV* a/w microscopic *hematuria*, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine—Anti GBM disease. *ALports syndrome (Anterior Lenticonus), Nail patella syndrome.*



Figs. 21.67A to C: Diabetic nephropathy (A. H and E stain B. diagrammatic and C. PAS stain), nodular glomerulosclerosis shows oval nodules of mesangial matrix at the periphery of glomerulus; C. nodules are PAS positive

Fibronectin Nephropathy

- *Autosomal dominant*; presents with proteinuria and progressive loss of renal function.
- Glomerulus shows *massive mesangial expansion* by *PAS positive deposits*.
- Special stains for amyloid (silver and Congo red) are *negative*.
- NO specific changes in renal tubules, interstitium and blood vessels.
- Glomeruli dot NOT stain for immunoglobulin or complement components.

Dent's Disease

- *X-linked* defect in the *chloride CLCN5 channel*; disorder of renal tubule characterized by:
 - Low molecular weight proteinuria,
 - Hypercalciuria,
 - Nephrolithiasis, nephrocalcinosis,
 - Hypophosphatemia,
 - Osteomalacia and
 - Renal insufficiency: *Renal failure* occurs in 2/3 of patients.
- Treatment is by *thiazide diuretics* to decrease urinary calcium excretion.

Atheroembolic Renal Disease

- MC in *males* with a h/o *DM, HTN, and IHD*.
- Precipitating events: *angiography, vascular surgery, anticoagulation* with heparin, *thrombolytic* therapy, or *trauma*.
- Clinically: seen *between 1 and 14 days* after the inciting event; *fever, abdominal pain, worsening hypertension and weight loss*; skin manifestations include *livedo reticularis* and *localized toe gangrene*.
- Labs: *rising creatinine, transient eosinophilia, elevated ESR, and hypocomplementemia*.
- *Definitive diagnosis* is by *kidney biopsy*: demonstrating microvessel occlusion with cholesterol crystals that leave a *"cleft" in the vessel*.
- *No effective therapy* is available; *withdrawal of anticoagulation* is recommended.

Bartter and Gitelman syndrome

Bartter syndrome	Gitelman syndrome
Site of Mutation: Na ⁺ – K ⁺ – 2Cl [–] cotransporter, K ⁺ channel (ROMK), or Cl [–] channel of thick ascending limb of Henle (hypofunction), barttin.	Site of mutation: Thiazide-sensitive Na-Cl cotransporter in DCT

Contd...

Bartter syndrome	Gitelman syndrome
Hypokalemic alkalosis with Hypomagnesemia polyuria and polydipsia, HYPERcalciuria (increased urinary calcium excretion); Nephrocalcinosis	Hypokalemic alkalosis with Hypomagnesemia Marked HYPOcalciuria, Chondrocalcinosis (an abnormal deposition of calcium pyrophosphate dihydrate (CPPD) in joint cartilage)

EXTRA EDGE

- Both Bartter and Gitelman are normotensive, non-edematous

Renal TB

- TB of the urinary tract arises from *haematogenous infection* from a distant focus. The lesions are usually *unilateral*.
- Kidney is progressively replaced by caseous material (*putty kidney*), which may be calcified (*cement kidney*). At any stage, the plain X-ray may show areas of calcification (*pseudocalculi*).
- Renal TB is often a/w TB of the bladder.
- In men, *tuberculous epididymo-orchitis* may occur without apparent infection of the bladder
- Renal TB usually occurs *between 20 and 40 years* of age, and is **MC in men**
- *Urinary frequency* is often the *earliest symptom* and may be the only one.
- *'Sterile' pyuria*: Routine urine culture is negative but there are white cells in the urine.
- *Painful micturition* is a feature of tuberculous cystitis.
- In 5% of cases, the first symptom is *haematuria* occurring from an ulcer on a renal papilla
- Treatment is by ATT.

RENAL TUBULAR ACIDOSIS (RTA)

- There are 4 types, only 3 are clinically important. Type 3 is uncommon and seen only in children. It is a non-anion gap metabolic acidosis.

- Type 1 (distal) RTA**
- Hypokalemic hyperchloremic metabolic acidosis and is due to selective *deficiency in H⁺ secretion* in the *distal nephron*.
 - Despite acidosis, *urinary pH cannot be acidified* and is *always above 5.5*; ↓ K⁺
 - *Etiology*: Renal stones, hereditary, amphotericin, cirrhosis, collagen vascular disease (SLE, Sjogren's, chronic active hepatitis)

Contd...

Contd...

Contd.

- Treatment: *potassium citrate*
 - Complications: nephrolithiasis
 - "Type **ONE** – **SiONE**"
- Type 2 (proximal) RTA**
- Hypokalemic hyperchloremic metabolic acidosis due to a selective **defect in the proximal tubule's ability to adequately reabsorb filtered HCO_3^-** ; $\downarrow \text{K}^+$
 - **Etiology:** Carbonic anhydrase inhibitors (acetazolamide, *Diamox*); hereditary; **Fanconi's syndrome** (defects of absorption in the proximal tubule, resulting in glucosuria, aminoaciduria, phosphaturia, and uricaciduria).
 - **Treatment:** potassium citrate
 - **Complications:** rickets, osteomalacia
 - "DI-hard Fon of type 2"
- Type 4 (hyperkalemic distal) RTA**
- MC type of RTA
 - **HYP**Oreninemic **HYP**Oaldosteronism \rightarrow defects in Na^+ absorption, H^+ and K^+ excretion, \downarrow ammoniogenesis; $\uparrow \text{K}^+$
 - **Etiology:** MC found in diabetic nephropathy, tubulointerstitial renal diseases, hypertensive nephrosclerosis, drugs (ACE inhibitors, NSAIDs and heparin) and AIDS; **acquired disorder**
 - **Treatment:** furosemide, kayexalate
 - **Complications:** hyperkalemia

More Important Points

- **Acute gouty arthritis in lead nephropathy is 'saturnine gout'**
- **Isolated microscopic hematuria of glomerular origin** is seen in **hereditary nephritis**.
- **Tubulointerstitial injury** is the MC form of renal involvement in Sjogren's syndrome.
- The clinical correlate of glomerular amyloid deposition is nephrotic range proteinuria.

CONNECTIVE TISSUE DISEASES

AUTOANTIBODIES IN CONNECTIVE TISSUE DISEASES

Disease	Immunologic marker	Comments
SLE	ANA (95% sensitivity)	<ul style="list-style-type: none">• Best screening test• A negative test virtually excludes SLE• Also positive in drug induced lupus, RA, scleroderma, Sjögren's syndrome
	Anti-dsDNA antibodies (60% sensitivity)	<ul style="list-style-type: none">• High titers correlate with nephritis and clinical activity• Decreasing titer correlates with worsening renal disease

Contd.

- Analgesic nephropathy is characterized by papillary necrosis and tubulointerstitial inflammation.
- **Transitional cell Ca** may develop in urinary pelvis or ureters as a long-term complication of **analgesic abuse**.
- **Hematospermia**, the presence of blood on the ejaculate results from inflammation of the prostate or seminal vesicles.
- Conditions a/w renal vein thrombosis = Pregnancy/Oral contraceptives; Invasion by renal cell carcinoma, Nephrotic syndrome; Trauma; Extrinsic compression (tumors, aortic aneurysm, lymph nodes); Dehydration (in infants) ("**POINTED**").
- **Chinese herbs nephropathy** (CHN) and **Balkan endemic nephropathy** (BEN) are chronic tubulointerstitial renal diseases a/w **urothelial carcinoma**. Both have been linked to exposure to **aristolochic acid**, a powerful nephrotoxin and human carcinogen.
- Only 6–12% of the original filtered uric acid is excreted in the urine, which amounts to **400–800 mg excreted** in the urine daily.
- **Sezior-Löken syndrome** = Nephronophthisis + **retinitis pigmentosa**; Other associated syndromes are **Joubert's syndrome** and **Burdet-Biedl syndrome**.
- Quantitative cultures are necessary for laboratory diagnosis in infection of UTI.
- **Intermittent hydronephrosis (Dietl's crisis):** Loins swelling is associated with acute renal pain. The pain goes and the swelling disappears when a large volume of urine is passed.
- Investigation of choice in renovascular hypertension is MRA (Magnetic Resonance Angiography).
- 'Sandy patches' in the urinary bladder are the result of calcified dead ova of **Schistosoma mansoni** with degeneration of the overlying epithelium
- 'Moth eaten' appearance of GBM in EM is seen in nail patella syndrome.
- A 'ring sign' on the pyelogram is pathognomonic of **papillary necrosis**.
- "Myeloid bodies" on EM of renal biopsy are seen in **Fabry's disease**.

Contd.

Disease	Immunologic marker	Comments
Drug Induced Lupus	Anti-Smith (Anti-Sm) antibodies	• SLE specific
Diffuse systemic sclerosis	Anti-histone antibodies	• Highly specific for drug induced lupus
Limited scleroderma (CREST syndrome)	Anti-topoisomerase I (Scl-70); Anti-RNA polymerase III	
Mixed Connective Tissue disease (MCTD)	Anti-centromere antibodies	• Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly, Telangiectasia (limited scleroderma)
Sjögren's syndrome	Anti-ribonucleoprotein (Anti-RNP)	
Rheumatoid arthritis	Anti-Ro (SS-A) Anti-La (SS-B)	• If Anti-Ro positive in SLE, risk of neonatal lupus and congenital heart block
Polymyositis or dermatomyositis	Rheumatoid Factor, RF (70% sensitivity, NOT specific) Anti-CCP (Cyclic Citrullinated Peptides) ANA Anti-Jo-1 antibodies	• HLA-DR4 common; titre does not correlate with disease activity • Specific for rheumatoid arthritis

EXTRA EDGE

- Immunofluorescent antibody test using **HEp-2 cells** is still considered the **gold standard** for screening of autoantibodies in rheumatology, and most of specific autoantibodies are currently tested by ELISA as a next step.

Appearance on IIF using Hep 2 cells	Associated antibody
Homogenous	Anti ds DNA Anti-histone Anti-chromatin
Speckled	Anti-Sm Anti-SSA (Ro); Anti-SSB (La) Anti-RNP Anti-Scl70

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- A **multisystem autoimmune disorder** involving auto-antibodies that affect multiple body systems. Antibody-mediated cellular attack occurs with the deposition of antigen-antibody complexes in the affected tissues
- **Risk factors:** **young female**, **African**, **Asian heritage**.

Criteria for the classification of SLE

- A patient is classified as having SLE if any **4 or more criteria** are met
- **Malar rash** (**Butterfly rash**); **Discoid rash**; **Photosensitivity**
 - Oral ulcers
 - Arthritis
 - **Serositis**
 - **Kidney disease:** > 0.5 g/d proteinuria, or $> 3+$ dipstick proteinuria, or Cellular casts
 - **Neurologic disease:** Seizures, or Psychosis (without other cause)

Contd.

Contd...

Criteria for the classification of SLE

- **Hematologic** disorders: Hemolytic anemia, or Leukopenia ($< 4000/\text{mCL}$), or Lymphopenia ($< 1500/\text{mCL}$), or Thrombocytopenia ($< 100,000/\text{mCL}$)
- **Immunologic** abnormalities: Positive LE cell preparation, or antibody to native DNA, or antibody to Sm, or False-positive serologic test for syphilis
- **Positive ANA**
- **Other features:** **Wire loop lesions** in kidneys (**Class IV**, lupus nephritis, **diffuse proliferative lupus nephritis**); **cytoid bodies** in retina, **Libman Sacks endocarditis**; **shrinking lung syndrome**; valvular heart disease (**mitral regurgitation MC**).



Fig. 21.68: Lupus nephritis showing glomerulus with "wire-loop" lesions due to extensive subendothelial deposition of immune complexes



Fig. 21.69: Butterfly rash in the malar area sparing nasolabial fold in SLE

Kidneys in SLE

Up to 50% of SLE patients have clinically significant renal involvement.

- Class I - Minimal mesangial lupus nephritis (**least common**)
- Class II - Mesangial proliferative lupus nephritis
- Class III - Focal lupus nephritis (< 50% glomeruli involved)
- Class IV - Diffuse lupus nephritis (**Most common** and most severe; **wire loop** lesions seen)
- Class V - Membranous lupus nephritis
- Class VI - Advanced sclerosing lupus nephritis

Tests:

- Anemia (*normocytic normochromic*), leukopenia, Thrombocytopenia
- Low complement (\downarrow C3 and C4 levels).
- \uparrow BUN and creatinine reflect renal involvement
- \uparrow ESR and CRP
- ANA is positive in 95% of patients, sensitive but not specific
- **Anti-dsDNA antibodies**—very specific, poor prognosis
- **Anti-Sm antibodies** are a **highly specific** finding but lack sensitivity for the diagnosis of SLE
- **Antihistone** antibodies seen with **drug-induced lupus**.
- Patients frequently have a **false-positive test for syphilis**
- **LE cell**: a phagocytic leucocyte (**macrophage or neutrophil**) that has engulfed the denatured nucleus of an injured cell. Demonstration of LE cell in vitro was used as a test for SLE >

Remember about SLE!

- MC **cardiac** manif of SLE = **Pericarditis**.
- MC **respiratory** manif of SLE = Pleurisy with/without effusion
- MC **hematologic** manif of SLE = Anemia.
- Most **SERIOUS** manif of SLE = nephritis.

Treatment:

- Avoid prolonged sun exposure and stress
- NSAIDs; Hydroxychloroquine (for dermatologic and (mild) renal symptoms)
- **Corticosteroids** for more severe forms of the disease
- Immunosuppressants (e.g. cyclophosphamide, methotrexate) are used in cases resistant to corticosteroids.

Outcomes:

- **Lupus anticoagulant** and **anticardiolipin** antibodies increase the risk of miscarriage and fetal death
- Coagulopathy may develop predisposing patients to thrombus formation, CVA, and cardiac events

Drug Induced Lupus

Main features which differentiate it from SLE are:

- The **sex ratio** is nearly **equal**
- **Nephritis and CNS** features are **rare**
- **Hypocomplementemia** and **antibodies to double-stranded DNA** are **absent**
- The clinical features and most laboratory abnormalities usually **revert toward normal when the offending drug is withdrawn**.

Etiological Drugs

- Antiarrhythmics: Procainamide, disopyramide, and propafenone
- Anti-HT: Hydralazine, ACE inhibitors and beta blockers
- Antibiotics: Sulfonamides, minocycline, isoniazid, rifabutin, Propylthiouracil
- Chlorpromazine and lithium
- Carbamazepine and phenytoin
- Sulfasalazine
- Hydrochlorothiazide
- Statins: Lovastatin and simvastatin; and
- IFNs and TNF inhibitors.

Polymyositis/Dermatomyositis

- See **dermatology chapter** for details (Pg 1063).

RHEUMATOID ARTHRITIS

- Autoimmune joint/tendon inflammation
- MC in **women**, **HLA DR4** association
- **Synovial hypertrophy** with **granulation tissue formation over cartilage (pannus)**
- Symmetrical **small joint pains (MCP and PIP, never DIP, wrists, knees, ankles)**
- **Early Morning stiffness** for 1 hour (gets better with exercise)—an important sign of **active inflammatory joint disease**.

- **Rheumatoid factor (IgM antibody to IgG)** are present in 70–80%; can be a/w false positives (see full details below under Rheumatoid Factor topic).
- Antibodies to **Cyclic Citrullinated Peptides (anti-CCP)**—**most specific test**

Deformities in RA

- **Ulnar deviation** of fingers, trigger fingers
- MCP hypertrophy
- **Swan neck deformity** (Hyperextension of the PIP joint with flexion of the DIP joint)
- **Boutonniere deformity** (flexed PIP and hyperextended DIP)
- **Z-line deformity** (subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint)
- **Atlantoaxial subluxation** most dangerous; **Cervical spine** MC involved **piano key** deformity (**distal radio-ulnar joint** subluxation)
- **Windswept deformity** (**genu valgum** of one knee and **genu varum** of other knee)
- **Pes Planovalgus** (flat feet)

- **Low synovial complement levels**

- X-ray:

- **Juxta-articular osteoporosis** (**earliest X-ray sign**);
- **Joint erosions**, and **joint space narrowing**.
- X-rays of **both hands** are useful for diagnosis.

- The **pathologic hallmarks** of RA are **synovial inflammation** and proliferation, **focal bone erosions**, and **thinning of articular cartilage**.



Fig. 21.70: Flexion at DIP joint with hyperextension at PIP joint in RA (Swan neck deformity)



Fig. 21.71: Boutonniere deformity in RA—flexion at PIP joint with extension at DIP joint

Systemic features of RA

- Ocular: **Scleritis** (RA is MC cause of scleritis); Uveitis, **Dry eyes**; Episcleritis
- **Subcutaneous nodules** (seen in 20%)
- **Carpal tunnel syndrome**
- Fever
- Respiratory: **Pleuritis** and **pleural effusion** (MC lung disease in RA) and Interstitial lung disease
- CVS: **Pericarditis** (MC cardiac disease in RA); Aortitis and aortic regurgitation;
- **Anemia of chronic disease (normocytic, normochromic)**
- **Felty syndrome (splenomegaly + neutropenia + severe destructive RA)**
- **Caplan's syndrome** (rheumatoid + coal worker's pneumoconiosis)

Rheumatoid Factors

- **Rheumatoid Factor (RF) = IgM autoantibodies** reactive with the **Fc portion of IgG**.
- RF is found in **> 2/3 of adults** with **Rheumatoid Arthritis (RA)**.
- The presence of RF is **not specific for RA**, as RF is found in 5% of healthy persons. RF in the general population increases with age >65 years.
- The presence of RF **does not establish the diagnosis of RA** as the predictive value of the presence of rheumatoid factor in determining a diagnosis of RA is poor. Therefore, the **RF test is not useful as a screening procedure**.
- However, the **presence of RF can be of prognostic significance because** patients with high titers tend to have more severe and progressive disease with extraarticular manifestations. RF is uniformly found in patients with nodules or vasculitis.
- **In summary**, a test for the presence of rheumatoid factor can be employed to confirm a diagnosis in individuals with a suggestive clinical presentation and, if present in high titer, to designate patients at risk for severe systemic disease.

Rheumatoid factor (RF) is also present in

- Connective tissue diseases: SLE, Sjögren's syndrome
- Lung disease: Sarcoidosis, Interstitial pulmonary fibrosis
- Chronic liver disease
- Infections: Infectious mononucleosis, Hepatitis B, Tuberculosis, Leprosy, syphilis, subacute bacterial endocarditis
- Parasitic: Visceral leishmaniasis, schistosomiasis, and malaria
- Transiently in normal individuals after vaccination or transfusion and may also be found in relatives of individuals with RA

EXTRA EDGE

- Above conditions can be remembered as the mnemonic: **"HIT LIST"** (see below)
 - Hepatitis B
 - Infectious mononucleosis
 - Tuberculosis
 - Leprosy
 - Leishmaniasis (Visceral)
 - Liver disease (chronic)
 - Infections - malaria
 - SLE
 - Sjögren's syndrome
 - Sarcoidosis
 - Syphilis
 - Subacute bacterial endocarditis
 - Schistosomiasis
 - Transiently after vaccination (in normals) or after Transfusion

SYSTEMIC SCLEROSIS

- Diffuse cutaneous SSc (dcSSc)** presents with progressive skin induration (scleroderma), starting in the fingers and ascending from distal to proximal extremities, the face, and the trunk.
- dcSSc** patients are at risk for **early pulmonary fibrosis** and **acute renal involvement**.
- In **limited cutaneous SSc (lcSSc)**—80% patients, patients generally have long-standing Raynaud's phenomenon before other manifestations of SSc appear. Skin induration is limited to the fingers (sclerodactyly), distal extremities, and face, and the trunk is NOT affected.

CREST and POEMS

- A subset of patients with lcSSc have **CREST syndrome**:
 - Calcinosis cutis
 - Raynaud's phenomenon
 - Esophageal dysmotility
 - Sclerodactyly, and
 - Telangiectasia
- POEMS syndrome**:
 - Polynuropathy
 - Organomegaly (liver, spleen, lymph nodes),
 - Endocrinopathy (gynecomastia, impotence, amenorrhea),
 - Production of **M** protein,
 - Skin changes (hyperpigmentation, **sclerodermatous** changes, hirsutism, hyperhidrosis, angiomas).

- Salt-and-pepper appearance** is characterized by the presence of **vitiligo-like depigmentation** with **perifollicular pigmentary retention**.
- Raynaud** phenomenon and antinuclear antibodies (ANA) are present in **virtually all patients of SSc**.
- Systemic features** of Scleroderma:

- Gastroesophageal reflux**
- Hypomotility** of GIT
- Pulmonary fibrosis
- Pulmonary hypertension
- Renal involvement.
- Scleroderma renal crisis**, usually a/w HTN, is a marker for a poor outcome; treat effectively with **ACE inhibitors**.
- Pulmonary involvement** is the **leading cause of death** in systemic sclerosis (Note: **In rheumatoid arthritis, CVS is MC cause of death**)

Features	Limited cutaneous SSc	Diffuse cutaneous SSc
Skin involvement	Limited to fingers, distal to elbows, face; slow progression	Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Precedes skin involvement; associated with critical ischemia	Onset contemporaneous with skin involvement
Pulmonary fibrosis	May occur, moderate (35%)	Frequent, early and severe (65%)
Pulmonary arterial Hypertension	Frequent, late, may be isolated	May occur, associated with pulmonary fibrosis
Scleroderma renal crisis	Very rare (2%)	Occurs in 15%; early
Calcinosis cutis	Frequent, prominent	May occur, mild
Autoantibodies	Anticentromere	Anti-topoisomerase I (Scl-70); Anti-RNA polymerase III

BEHCET'S DISEASE

- Behcet's affects young males/females from **Mediterranean, Middle East, Far East (Japan)**
- Linked with **ancient Silk Route**
- M: F = 1:1, BUT **males often have more severe disease, Blacks rarely affected**.
- A/w with **HLA-B5 (B51)** (NOT HLA B27!).
- Treatment: **Cyclosporine, azathioprine, interferon alfa**, and treat the uveitis.

Diagnostic Criteria of Behçet's Disease: Essential criteria plus two of the non-essential criteria.

Essential criterion	Non-essential criteria
Recurrent Oral Ulcers	Recurrent genital ulcers
Painful	
▪ Shallow or deep with a central yellowish necrotic base	▪ Less common than oral ulcers but More Specific
	▪ DO NOT affect the glans penis or urethra, and produce scrotal scars

Contd...

Contd...

Diagnostic Criteria of Behçet's Disease: Essential criteria plus two of the non-essential criteria.

- Appear singly or in crops
- Located anywhere in the oral cavity
- Persist for 1–2 weeks and subside **without leaving scars**
- Skin lesions**
 - Folliculitis
 - Erythema nodosum
 - Acne-like** exanthema
 - Vasculitis (infrequently)
- Pathergy test**
 - Pustule formation at site of sterile needle prick after 24-48 hours is a common and **SPECIFIC** manifestation
- Eye lesions**
 - Hypopyon uveitis** (SPECIFIC but RARE manifestation)
 - Bilateral panuveitis
 - Iritis, posterior uveitis
 - Retinal vessel occlusions, and optic neuritis

EXTRA EDGE

- Other causes of **hypopyon uveitis** include **infectious endophthalmitis, sarcoidosis, retinoblastoma, metastatic tumors, rifabutin and masquerade syndromes**.

Features of vasculitis

Vasculitis	Pathology	Clinical features
Giant cell (temporal arteritis)	Segmental granulomatous inflammation with intimal thickening and internal elastic lamina fragmentation	Have been described in detail under CNS in this medicine chapter above. Involves temporal artery and other arteries of head (vertebral, ophthalmic and carotids)
Takayasu's arteritis (Pulseless disease)	Chronic vasculitis affecting aorta and its branches - ' aortic arch syndrome '; pulmonary, coronary and renal artery maybe involved	Young Asian females ; Aortic root dilation → aortic insufficiency ; vascular insufficiency of upper extremities with cold/numb fingers; peripheral pulses absent ; BP in LL > UL (reverse coarctation); maybe a/w HTN; Subclavian artery MC involved.
Polyarteritis nodosa (PAN)	Type II hypersensitivity (immune complex mediated) reaction with transmural necrotising inflammation and fibrinoid necrosis ; transmural inflammation ; Renal and visceral arteries affected - pulmonary artery NOT affected	Heart – Coronary Artery disease leading to ischemia; Kidneys – HTN, glomerulonephritis, hematuria; GIT – abdominal pain, diarrhea, melena; Musculoskeletal – myalgia, arthralgia, weakness; a/w Hepatitis B virus in 30% cases; Classic PAN is ANCA negative .
Kawasaki's disease (mucocutaneous lymph node syndrome)	Transmural inflammation leading to aneurysm formations; can include coronary artery - coronary aneurysms	Affects children ; Fever, conjunctivitis, mucus membrane ulcers, lymphadenopathy; treat with high dose aspirin . Infantile polyarteritis nodosa is very similar to Kawasaki disease

Contd...

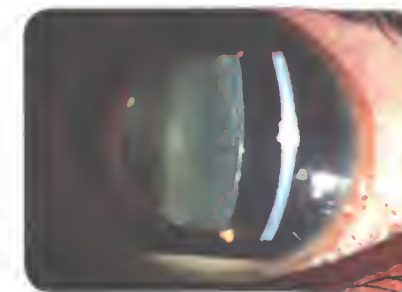


Fig. 21.72: Acute iridocyclitis—hypopyon

VASCULITIS

Classification of Primary Vasculitis

Predominantly large vessel vasculitis

- Takayasu's arteritis
- Giant cell (temporal) arteritis
- Behcet's disease

Predominantly medium vessel vasculitis

- Polyarteritis nodosa
- Buerger's disease (Thromboangiitis obliterans, TAO)

Predominantly small vessel vasculitis

- ANCA-associated disorders
 - Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
 - Microscopic polyangiitis
 - Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)

Contd...

Vasculitis	Pathology	Clinical features
Thromboangiitis obliterans (Buerger's disease)	Segmental vasculitis with thrombosis (containing microabscesses) ; may spread to adjacent veins and venules	Smokers affected; painful ischemia of extremities resulting in chronic ulcers on toes, feet and fingers
Granulomatosis with polyangiitis (Wegener's granulomatosis)	Necrotizing granulomas of upper and lower respiratory tract, lungs ; necrotizing (often crescentic, RPGN) glomerulonephritis	Recurrent inflammatory sinusitis , ulcers of nose, palate and pharynx ; strawberry gingivitis , Scleritis , PR-3 ANCA (c-ANCA) +ve in 95% cases
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Eosinophilic vasculitis	Asthma, allergic rhinitis , lung infiltrates, hyper-eosinophilia ; MPO-ANCA (p-ANCA) +ve in 50% cases
Microscopic polyangiitis (hypersensitivity vasculitis)	Leukocytoclastic destruction of the vessels and focal bleeding, often ass. with glomerulonephritis	Presents with non-blanching/palpable purpura, often related to drug hypersensitivity; MPO-ANCA (p-ANCA) +ve in 80% of cases.

EXTRA EDGE

- Anti-Proteinase-3 (**PR3-ANCA, previously c-ANCA**) is a/w Wegener's granulomatosis (granulomatosis with polyangiitis). (**Wegener's = c-ANCA; We ANI**).
- Anti-myeloperoxidase (**MPO-ANCA, previously p-ANCA**) is a/w Churg-Strauss and microscopic polyangiitis
- **Anti-endothelial cell antibodies** are a/w **Kawasaki disease**.
- **Schamberg's purpura**: progressive **pigmented purpura on legs** and feet due to **lymphocytic capillaritis**; **cayenne pepper purpuric spots** are seen.

Palpable Purpura

Palpable purpura is a raised, non-blanchable erythema and signifies extravasation of RBCs outside of blood vessels. Causes are

Vasculitides

- Henoch-Schonlein purpura
- Essential mixed cryoglobulinemia
- Wegener's granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Leukocytoclastic vasculitis
- Polyarteritis nodosa

Emboli

- Acute meningococemia
- Disseminated gonococcal infection
- Rocky Mountain spotted fever
- Ecthyma gangrenosum

SPONDYLOARTHROPATHIES

These disorders are noted for:

- Striking a/w **HLA-B27**
- **Male** predominance
- Onset usually **before age 40**

- Inflammatory arthritis of the spine or the large peripheral joints (or both)
- **Enthesopathy** (inflammation of where ligaments, tendons, and joint capsule insert into bone)
- **Uveitis** in a significant minority
- **Absence of rheumatoid factor** in the serum (*hence 'seronegative'!*)

Seronegative (HLA B27) spondyloarthropathies are:

- Reactive arthritis (**Reiter syndrome**)
- Ankylosing spondylitis
- Psoriatic arthritis [see under **Dermat** chapter (Pg 1044)]
- Arthritis a/w inflammatory bowel disease
- Undifferentiated spondyloarthropathy

Reactive Arthritis (Reiter's Syndrome)

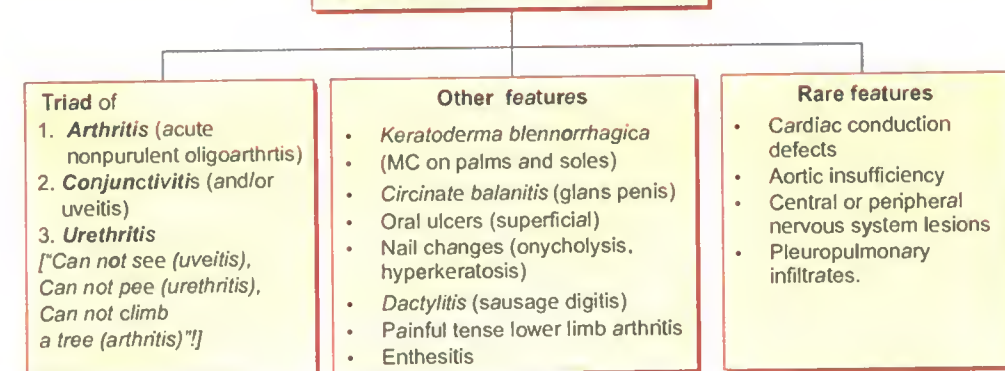
- **HLA B27 positive** seronegative spondyloarthritis.
- Arthritis following gastroenteritis or urogenital infections
- Triggered by *Shigella*, *Yersinia*, *Chlamydia*, *Salmonella* and *Campylobacter*
- MC by ***Shigella flexneri***.
- Constitutional symptoms are common, including fatigue, malaise, fever, and weight loss. (See flowchart below)

Ankylosing Spondylitis (AS)

- Synonyms: **Marie Strumpell disease**, **Bechterew disease**
- **HLA B27** associated in **90% cases**.
- **Bony ankylosis** of spine – "**bamboo spine**".
- Affects **young adults**, **low back pain** and **limitation of flexion and extension of lumbar spine** is prominent.
- **Schober test** is useful measure of lumbar spine flexion.

- X-rays–More under radiodiagnosis chapter (Pg 1163).
- Extra-articular manifestations:
 - **Acute anterior uveitis** (**most common**, occurs in 40%, can antedate the spondylitis)

➤ Inflammatory bowel disease, cauda equina syndrome, upper pulmonary lobe fibrosis, aortic insufficiency, retroperitoneal fibrosis, prostatitis, amyloidosis.

Reiter's syndrome – clinical features**SJÖGREN SYNDROME**

- Sjögren syndrome is a systemic chronic autoimmune inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs (lacrima and salivary glands).
- Sicca symptoms include:
 - **Xerophthalmia** (dry eyes)
 - **Xerostomia** (dry mouth)
 - **Xeroderma** (dry skin) and
 - **Parotid gland enlargement**
- **Primary** Sjögren syndrome occurs in the absence of any another underlying rheumatic disorder
- **Secondary** Sjögren syndrome is a/w another underlying rheumatic disease, such as SLE, RA or scleroderma.
- Classic clinical features of Sjögren syndrome may ALSO be seen in infections with certain viruses - **HCV; HIV and HTLV**.
- Treatment is largely symptomatic (e.g. lotion for dry skin, artificial tears for dry eyes). **Rituximab** has shown promise in the treatment of severe extraglandular manifestations (e.g. **vasculitis, cryoglobulinemia, peripheral neuropathy**).

- **Biopsy of the lip** (to examine **minor salivary glands**) is essential for **diagnosis** of Sjögren syndrome.

Causes of Xerostomia (DRY Mouth)

Systemic causes	Local causes
<ul style="list-style-type: none"> • Autoimmune connective tissue disorders: Sjögren's syndrome, primary and secondary • Granulomatous diseases: sarcoidosis, tuberculosis • Graft-versus-host disease • Cystic fibrosis • Bell's palsy • Diabetes (poorly controlled) • Amyloidosis • Human immunodeficiency virus infection • Thyroid disease: Hypo- and hyper-thyroidism • Late stage liver disease • Affective disorder • Eating disorders and malnutrition • anorexia, bulimia, dehydration • Drugs: Anticholinergics 	<ul style="list-style-type: none"> • Salivary duct calculi (esp. submandibular duct) • Sialadenitis • Salivary gland aplasia • Post radiotherapy

ENDOCRINE SYSTEM

Signaling Pathways of Endocrine Hormones (Second Messengers)

Second messenger	Hormones
cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V2-receptor), MSH, PTH, Glucagon, GHRH, Catecholamines, Calcitonin "FLAT ChAMP"
cGMP	BNP (Brain natriuretic peptide); ANP (atrial natriuretic peptide), Nitric Oxide (EDRF) "BANG"
Phosphatidylinositol (PIP2) or inositol triphosphate (IP3)	GnRH, Oxytocin, Acetylcholine, TRH, Histamine, Angiotensin II, Gastrin, Vasopressin (V1, V3 receptors), CCK "GOAT HAG VCI"
Receptor tyrosine kinase	Insulin, IGF-1, FGF, PDGF, EGF
Intracellular receptors	Steroids (Glucocorticoids, mineralocorticoids, estrogens, progesterone, androgens), Thyroxine, Vitamin D (calcitriol) "STOI"

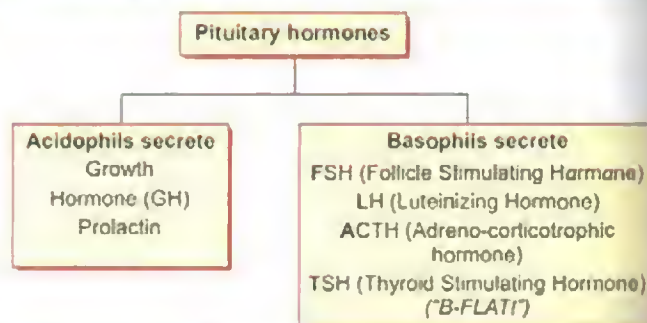
Oxytocin and Vasopressin

- **Oxytocin and Vasopressin (ADH)** are **nonpeptides** synthesized within the **supraoptic and paraventricular nuclei** of the hypothalamus and are transported down the axon and stored in the nerve endings within the neurohypophysis (posterior pituitary).
- Oxytocin **increases the force of uterine contraction**.
- Oxytocin is released during labor and the uterus is highly sensitive to it at this time. However it **does NOT appear to be obligatory for initiating parturition**—delivery occurs even in hypophysectomized animals and humans. It is only **facilitatory in action**.
- Stimuli for oxytocin secretion—coitus, parturition, suckling, etc.
- Stimuli for vasopressin secretion—water deprivation, hemorrhage, hypertonic saline infusion, etc.

PITUITARY GLAND

Pituitary gland is situated within the pituitary (hypophyseal) fossa which is also known as the **sella turcica** since it resembles a **Turkish saddle**.

- The anterior (**adenohypophysis**) and intermediate pituitary are a derivative of **Rathke's pouch** (oral ectoderm).
- The **anterior pituitary synthesizes and secretes FSH, LH, ACTH, TSH, GH, melanotropin (MSH), prolactin**. These hormones are released from the anterior pituitary under the influence of hypothalamus.
- The posterior pituitary (**neurohypophysis** or **pars nervosa**) develops from a **downgrowth** from the **floor of the third ventricle (diencephalon)**—neuroectoderm.
- **Vasopressin and Oxytocin**, made in the **hypothalamus** and shipped to the posterior pituitary.



EXTRA EDGE

- "With progressive lesions of the pituitary (compression or destruction), trophic **hormone failure** occurs sequentially **GH first > FSH > LH > TSH > ACTH last**".
- During childhood, **growth retardation is the presenting feature**, and in adults, **hypogonadism is the earliest symptom**.

Pituitary Adenoma

- **Microadenoma:** <1 cm in diameter and DO NOT usually invade the parasellar region; functioning adenomas—usually secrete hormones and cause syndromes.
- **Macroadenoma:** >1 cm in diameter and may be **locally invasive** and compress on adjacent structures—cause symptoms by mass effect—bitemporal visual loss, headaches etc.—nonfunctioning adenomas.
- **MRI** is the investigation of choice for pituitary adenomas.

Regulation of Growth Hormone Secretion

GH stimulated by	GH inhibited by
<ul style="list-style-type: none"> • Hypoglycemia • Fasting • Starvation • Exercise • Stress and trauma • Initial stages of sleep 	<ul style="list-style-type: none"> • Hyperglycemia • Increase in free fatty acids in blood • Later stages of sleep (REM sleep)

Acromegaly

- **↑↑ GH in adults**—from GH secreting **pituitary adenoma**.
- GH is the **most abundant pituitary hormone**.
- **Clinically:**
 - **Enlargement of head, fingers, feet, jaw (prognathism)**
 - **Coarse facial features**
 - **Large furrowed tongue**
 - **Deep voice**
 - **Impaired glucose tolerance (insulin resistance)**
 - **Intense sweating**
 - **Cardiomegaly**
 - **HTN**
 - **Joint abnormalities**
 - **Colonic polyps/colonic malignancy**.
 - **increased heel pad thickness** (>21.5 in females, >23 in males), **thickening of phalanges**, **generalized osteoporosis** are seen.

Tests for Acromegaly

- MRI to detect adenoma
- **Best initial/screening test:** ↑ IGF-1 (insulin-like growth factor) levels. GH levels is **not done first** since GH secretion is maximum in middle of night during sleep and GH has short half life.
- **Most accurate test:** Oral GTT – **failure of suppression of GH** to <1 µg/L within 1-2 h of an oral glucose load (75 g). (↑ GH is normal in stress, exercise and hypoglycemia; Oral glucose administration should normally suppress GH levels)

- Treatment:
 - **Transsphenoidal surgical removal** cures 70% cases.
 - **Carbergoline** or dopamine agonists (bromocriptine) **inhibit GH release**.
 - **Octreotide** and **lanreotide** (somatostatin analogues) **prevents GH release**.
 - **Pegvisomant:** GH receptor antagonist.
 - Stereotactic radiosurgery.



Fig. 21.73: Acromegaly male (45 years) side view. Note the prognathic mandible



Fig. 21.74: Acromegaly large hands. Note normal for comparison

Prolactinoma

- **MC pituitary tumor**
- **Clinically:**
 - **Women:** **Amenorrhea** and **galactorrhea in absence of pregnancy**; hence **women (get worried) present early!** Prolactin inhibits GnRH → If there is no GnRH, body cannot release FSH and LH
 - **Men:** **Impotence, decreased libido, sometimes gynecomastia**. Presents **late!** (since no man rushes in a panic to the doctor shouting "I can't get an erection and my breasts are big!"). Men are more likely to have **headache** and visual disturbance (**bitemporal hemianopia** due to **chiasmal compression**).
- **↑↑ Serum prolactin** (>200)
- Diagnosed by MRI brain
- Treat with **dopamine agonist: carbergoline** best tolerated; **bromocriptine** is alternative;
- Surgery ONLY IF no response to medical therapy.

Visual Field Defect in Chiasmal Compression

- Visual field defects depend on the anatomical relation between pituitary and optic chiasma.

Pituitary adenoma	Craniopharyngioma
<ul style="list-style-type: none"> • If chiasm is central both superotemporal fields are affected first (bitemporal superior quadrantanopia), as the tumor grows upwards and splay the anterior chiasmal notch compressing the crossing inferonasal fibers. • The defect then progresses into lower temporal fields and becomes a bitemporal hemianopia. 	<ul style="list-style-type: none"> • Initial defect involves both inferotemporal fields because the tumor compresses the chiasm from above and behind damaging the upper nasal fibers. • The defect then spreads upward to involve the upper temporal fields, and becomes a bitemporal hemianopia.

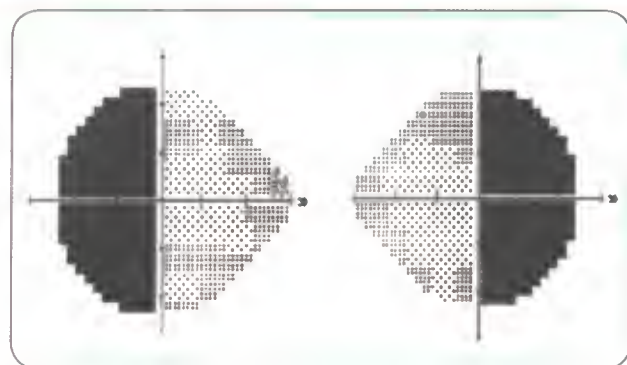
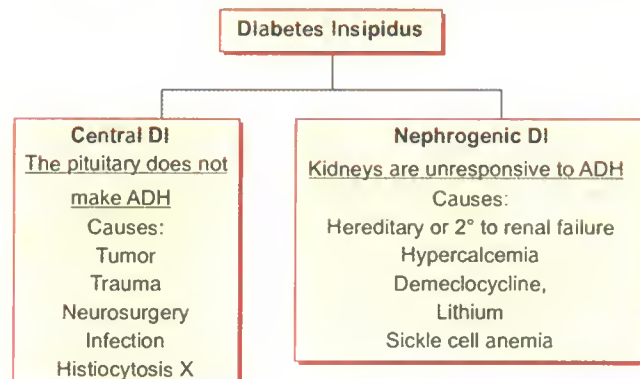


Fig. 21.75: Bitemporal

Diabetes Insipidus

- Characterized by **intense thirst and polyuria** with an inability to concentrate urine owing to a lack of ADH.



- Diagnosis:**
 - Water deprivation test**—Urine osmolality doesn't ↑ in nephrogenic DI.
 - Response to desmopressin**—distinguishes between central and nephrogenic DI—in **Central DI**, **urine osmolality should ↑ by 50%** in response to desmopressin (ADH analog).
 - Plasma:** Serum osmolality > 290 mOsm/L; ↑ Na⁺, **hypernatremia** (Serum Na⁺ < 135).
 - Urine:** specific gravity < 1.006, ↓ osmolality (< 300 mOsm/L).
- Treatment:** adequate fluid intake.
 - For **central DI**—intranasal **desmopressin is DOC**.
 - For **nephrogenic DI**—**hydrochlorothiazide, indomethacin or amiloride**.

Syndrome of Inappropriate Secretion of ADH (SIADH)

- Causes:**
 - Pulmonary**—TB, pneumonia, lung abscess
 - CNS:** meningitis, brain abscess, **head trauma**

- Drugs:** Cyclophosphamide, Chlorpropamide, Chlorbutate, Carbamazepine, Phenothiazine, Vasopressin/Desmopressin, Oxytocin (high doses), Nicotine, Vincristine, Tricyclics, MAO inhibitors, Serotonin reuptake inhibitors.
- Ectopic ADH production:** **small cell lung** (lymphoma, sarcoma, duodenal/pancreatic Ca).
- Clinically:**
 - Asymptomatic** unless serum sodium becomes very low (< 120 mEq/L).
 - Chronic nausea, weakness, progressive confusion
 - Plasma:** ↓↓ serum osmolality (i.e., **hypotonicity**), ↓ Na⁺.
 - Urine:** ↑↑ **urine Na⁺**; urine osmolality will be **higher than expected** for the coincident hyponatremia (> 100 mOsm/kg).
- Treatment:**
 - Fluid restriction** (free water consumption < 1L/day)
 - Vasopressin V2 receptor antagonist (conivaptan, tolvaptan)** are approved for euvolemic and hypervolemic hyponatremia in **SIADH**.
 - Furosemide** should be used for diuresis in symptomatic patients
 - Demeclocycline may be used in patients with chronic disease who do not respond to diuresis and fluid restriction
 - Hypertonic saline** may be used to correct **severe cases**.

Cerebral Salt Wasting

- Suspected when there is **hyponatremia in a hypotensive patient with associated CNS disease**.
- Lab features: Hypovolemia (clinical evidence of volume depletion), urine Na⁺ high, high urine flow rates, high urine osmolality and net sodium loss is very high.

Causes of Hypopituitarism

- Sheehan syndrome:** ischemic infarct of pituitary following **postpartum bleeding**; pregnancy induced pituitary growth leads to increased susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation and cold intolerance.
- Empty sella syndrome:** atrophy or compression of pituitary (which lies in sella turcica); often idiopathic, MC in obese women.
- Pituitary apoplexy:** sudden hemorrhage of pituitary gland, often in presence of pre-existing pituitary adenoma. Usually presents with sudden onset severe headache and hypopituitarism.
- Brain injury
- Radiation
- Craniopharyngioma.

THYROID GLAND

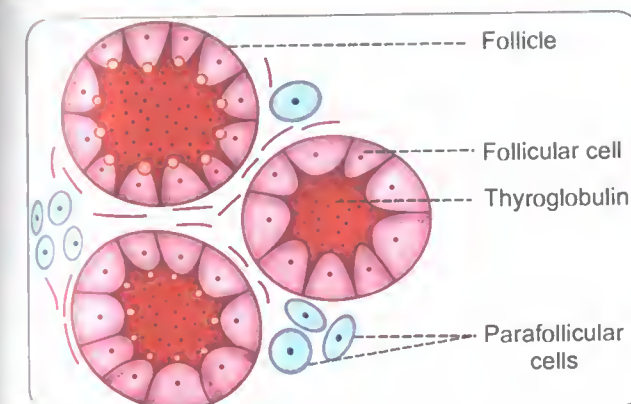


Fig. 21.76: Histology of thyroid gland

Thyroid Basics (Fig. 21.77)

- Thyroxine was extracted by EC Kendall in 1915.
- Normal thyroid gland weighs 20–25 g.
- Normal parathyroid gland weighs up to 50 mg.
- Total body iodine content** = 30–50 mg, out of which about 1/5 is present in the thyroid.
- Thyroid hormones are:
 - T4 (tetraiodothyronine OR thyroxine) and T3 (triiodothyronine)** secreted by **follicles** of thyroid
 - calcitonin** by **parafollicular C cells**

- Transport of thyroid hormones in blood**
 - Thyroid binding globulin (TBG)** is a glycoprotein that binds most T3/T4 in blood
 - Thyroid binding prealbumin or transthyretin (TBPA or TTR)** binds 25% and
 - Albumin transports about 10% of thyroid hormones
- ↓ TBG in **hepatic failure**; ↑ TBG in **pregnancy**.

EXTRA EDGE

- From the follicular cells, **iodine** is transported into the follicular cavity by an iodide-chloride pump called **pendrin**.
- Pendrin gene** is on **chromosome 7**: Mutations give rise to **Pendred's syndrome** characterized by **familial goiter, congenital sensorineural deafness** and **autosomal recessive**.
- Wolff-Chaikoff effect:** In normal individuals, large doses of iodides act directly on the thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis.

Function of Thyroxine = "4Bs"

- Bone growth promotion** (synergism with GH)
- Brain (CNS) maturation** during fetal growth
- Beta-adrenergic effects** (↑ cardiac output, heart rate, stroke volume, contractility)
- ↑ **Basal metabolic rate (BMR)** via ↑ Na⁺/K⁺ ATPase activity = ↑ O₂ consumption, resp. rate, ↑ body temperature.
- ↑ **glycogenolysis, gluconeogenesis, lipolysis**.

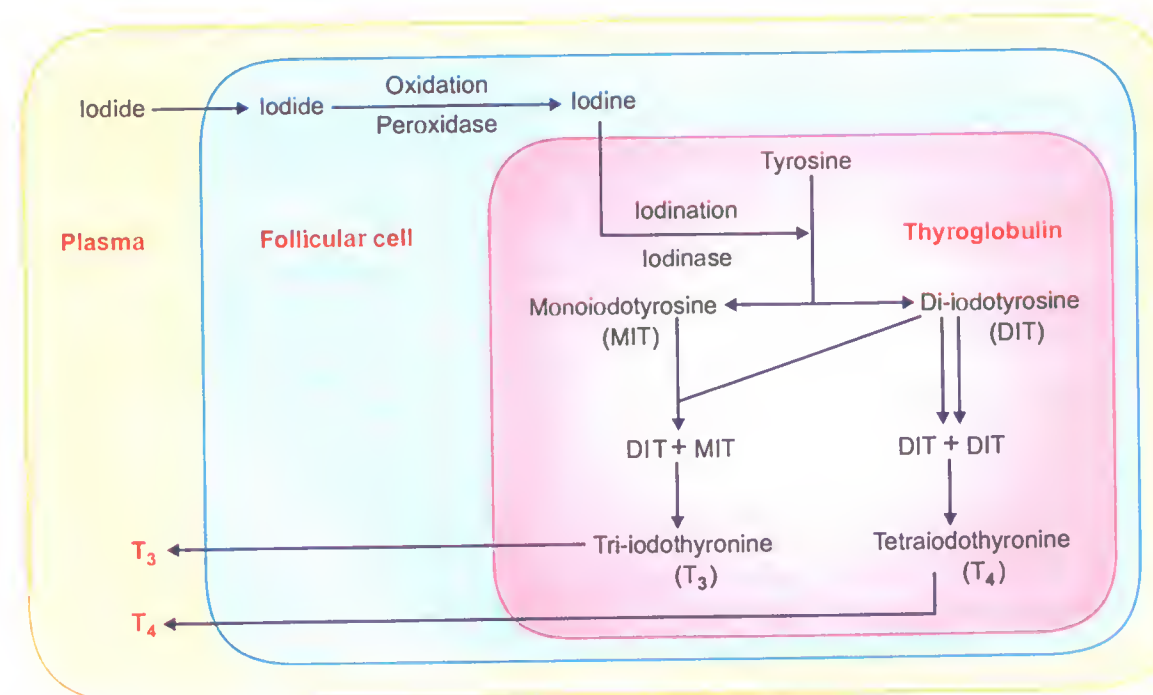


Fig. 21.77: Synthesis of thyroid hormones

Regulation of Thyroid Secretion (Fig. 21.66)

FNAC of Thyroid

- Fine-needle aspiration cytology (FNAC) is the *investigation of choice* in *discrete thyroid swellings*.
- Thyroid conditions that may be diagnosed by FNAC include:
 - Colloid nodules
 - Thyroiditis,
 - Papillary carcinoma,
 - Medullary carcinoma,
 - Anaplastic carcinoma and
 - Lymphoma.
- **FNAC is not very useful in follicular carcinoma as it is difficult to** differentiate it from follicular adenoma as *main feature in follicular Ca is capsular invasion/vascular invasion* which is not evident on FNAC.

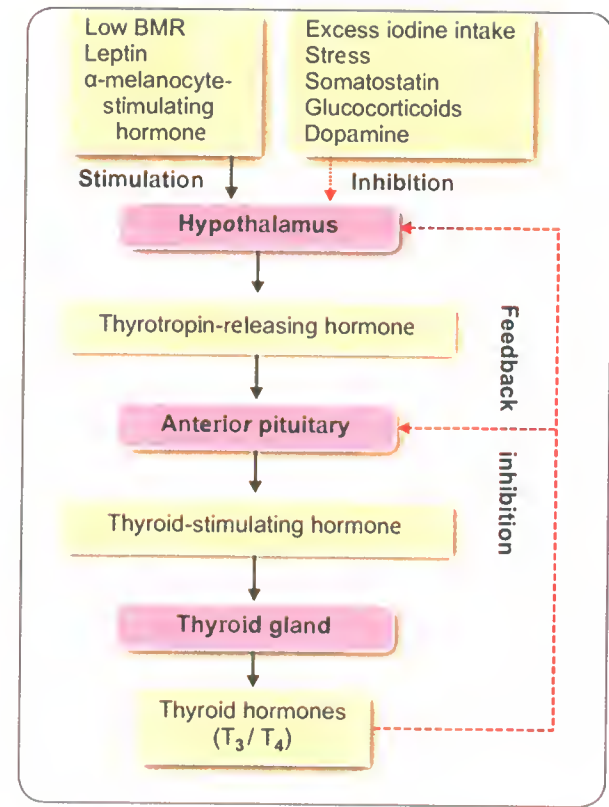


Fig. 21.78: Regulation of secretion of thyroid hormones

- FNAC results should be *reported using standard terminology* as below.

Thy1	Nondiagnostic
Thy1c	Nondiagnostic cystic

Thy2	Non-neoplastic
Thy3	Follicular
Thy4	Suspicious of malignancy
Thy5	Malignant

Graves' Disease (Thyrotoxicosis)

- **Graves disease** is the MC cause of *endogenous hyperthyroidism*.
- **Graves' disease** is the **MC cause of thyrotoxicosis** and results usually in *diffuse toxic goiter*.
- MC in *women*; M:F = 7:1; MC between 20-40 years of age:
 - A/w **HLA-B8, DR3** and DR2
 - **Smoking**—minor risk factor for Grave's but **strongly linked** with development of *ophthalmopathy*.
 - **Incidence of:**
 - Grave's ophthalmopathy—90% of Grave's patients
 - Graves' dermopathy - < 5%
 - Graves' acropachy - < 1%
- Grave's disease is due to **IgG antibodies directed against the TSH receptor** on the thyroid follicular cell, which stimulate thyroid hormone production and in the majority, goiter formation—these antibodies are termed **thyroid-stimulating immunoglobulins (TSI) or TSH-receptor antibodies (TRAb)** {earlier called *long acting thyroid stimulator (LATS)*} and can be detected in the serum of 80-95% of patients with Grave's disease.
- **TSI** is relatively **specific for Grave's disease, in contrast to thyroglobulin and thyroid peroxidase antibodies**.
- Lab tests: ↓ **TSH**, ↑ total T4, ↑ free T4, ↑ T3 uptake
- Clinically: Features of **Hyperthyroidism**
 - Heat intolerance
 - Hyperactivity
 - diarrhea, weight loss
 - tachycardia (*persists during sleep*),
 - **Crile's grading of sleeping pulse rate** in thyrotoxicosis: Grade I = < 90/min; Grade II = 90-110/min; Grade III = > 110/min
 - Hypertension
 - Fine resting tremor
 - Proptosis/exophthalmos (see thyroid eye disease topic below)
 - Warm sweaty skin
 - Irregular menses
 - Osteoporosis
 - Proximal myopathy
- Treatment: Antithyroid drugs as given separately below.

Clinical features of Hypothyroidism

- ↑ **TSH**, ↓ **total T4**, ↓ **free T4**, ↓ **T3 uptake**
 - Cold intolerance
 - Hypoactivity
 - Fatigue, lethargy,
 - Constipation, weight gain,
 - ↓ deep tendon reflexes,
 - Delayed relaxation of ankle jerks
 - Myxedema,
 - Dry cool skin and coarse brittle hair,
 - Bradycardia, heavy menstruation
 - Carpal tunnel syndrome
 - Treatment: Oral thyroxine 0.1 to 0.2 mg/day

EXTRA EDGE

- Drugs causing hypothyroidism/goiter as a side effect: Lithium; Amiodarone; Sulfonamides, para-aminosalicylic acid; Phenobarbitone, phenytoin, carba- mazepine, rifampin.

Differential Diagnosis

	Graves' disease	Subacute thyroiditis (de Quervain's; Giant Cell thyroiditis)	Hashimoto's disease
Etiology	Antibody to TSH receptor	Viral (possibly Coxsackie virus or Mumps)	Autoimmune
Clinically	Hyperthyroidism; diffuse painless goiter ; ophthalmic (proptosis , lid lag, conjunctival injection); pretibial myxedema	Hyperthyroidism → hypothyroidism. Painful tender thyroid gland ; jaw pain, granulomatous inflammation - epithelioid cells and multinucleated giant cells often containing colloid	Hypothyroidism ; painless thyroid enlargement; slow course, lymphocyte infiltrate with germinal centers, Hurthle cells on histology; may lead to lymphoma
Diagnosis	↑ RAIU	↓RAIU, ↑ ESR, thyroid antibodies are negative	antimicrosomal and antithyroglobulin antibodies
Treatment	Propylthiouracil, methimazole, thyroid ablation with I 131	NSAIDs, steroids if pain severe	Levothyroxine

Thyroid Eye Disease (TED)

- **Smoking** is major risk factor **TED**.
- **TED is the MC cause of unilateral and bilateral proptosis in adults**. MC in *females*.
- **Soft tissue signs: epibulbar congestion/hyperemia over insertions of horizontal recti; periorbital swelling; Superior limbic keratoconjunctivitis**.
- **Lid retraction**: possibly due to (1) *fibrotic contracture* of levator, (2) *secondary overaction* of the levator-superior rectus complex in response to hypotropia produced by fibrosis of inferior rectus muscle, (3) *sympathetic overstimulation of Muller's muscle* due to high levels of thyroid hormones. "**Scleral show**" indicates lid retraction.

- Infrequent blinking = **Stellwag sign**, (**Still** lids) - Mild, first sign to appear
- Lid Lag (**von Graefe** sign);
- Poor Forehead wrinkling on upgaze = **JoFfroy** sign;
- Convergence Weakness = **Moebius' sign** ("**W** = **reverse M**"); severe
- **LID** retraction = **Dalrymple** sign;
- Hyperpigmented **Lid** skin = **JellLinek** sign;
- Frightened, staring look = **Kochers** sign;
- "**Pseudo**" -**von Graefe** sign - upper eyelid may elevate with downward gaze, simulating lid lag - seen in **III cranial nerve palsy with aberrant regeneration**

- **Myopathy: restrictive myopathy** due to inflammatory edema and muscle fibrosis; **MC involved muscle is Inferior rectus**.

- On CT scan/US, *muscle belly is thickened BUT tendon is spared*—"cola bottle/coca cola sign" (in pseudotumor both belly and tendon involved!).
- Blinding complications of TED** = Optic N. compression, severe exposure keratopathy, glaucoma.
- Werner classification ("NO SPECS")**
 - Grade 0: No signs or symptoms
 - Grade 1: Only signs (lid retraction or lag), no symptoms
 - Grade 2: Soft tissue involvement
 - Grade 3: Proptosis (> 22 mm)
 - Grade 4: Extraocular muscle involvement (IR first, diplopia)
 - Grade 5: Corneal involvement
 - Grade 6: Sight loss.



Fig. 21.79: Primary thyrotoxicosis. Note the exophthalmos

- Riedel's thyroiditis**: Thyroid replaced by fibrous tissue → hypothyroidism
- Toxic multinodular goiter (Plummer's disease)**: Iodine deprivation followed by iodine restoration. Causes release of T3 and T4. Nodules are not malignant.
- Jod-Basedow phenomenon**: Thyrotoxicosis occurring when a patient with endemic goiter is given supplemental iodine OR moves to iodine-replete area.
- Cretinism**: Due to lack of dietary iodine → endemic goiter in children. Pot bellied, pale, puffy faced child with protruding umbilicus and tongue.

Painless Thyroiditis, or "Silent" Thyroiditis

- A/w autoimmune thyroid (clinical course similar to subacute thyroiditis); MC in women with type 1 DM;

may occur in women 3-6 months after pregnancy (*postpartum thyroiditis*).

- Typically, patients have a *brief phase of thyrotoxicosis* lasting 2-4 weeks (Rx with propranolol), followed by hypothyroidism for 4-12 weeks, and then resolution.
- In addition to the painless goiter, silent thyroiditis can be distinguished from subacute thyroiditis by a *normal ESR* and the *presence of TPO antibodies*.
- Glucocorticoid** treatment is *not indicated* for silent thyroiditis.

Treatment of Hypo/Hyperthyroidism

- Thyroid related rugs have been discussed in *pharmacology chapter (Pg 357)*.

Thyrotoxic Crisis (Thyroid Storm)

- A rare *life-threatening acute exacerbation of hyperthyroidism* that occurs when hyperthyroidism is incompletely treated or not treated and then significantly worsens in the setting of *acute illness* (e.g., stroke, infection, trauma, DKA), *trauma* or *post thyroid surgery storm* (manipulation of the thyroid gland during thyroidectomy *historically* caused a flood of hormone release, often resulting in highly toxic blood levels).
- Clinically**: Agitation, delirium, fever, diarrhea cardiac failure, tachyarrhythmia and coma.
- Management**: Measures that reduce thyroid hormone synthesis (4P's):
 - Propranolol** (non-selective beta blocker) - *most valuable measure*.
 - Propylthiouracil** - *antithyroid drug of choice*.
 - Potassium iodide** (Lugol's Iodine) given one hour after the first dose of propylthiouracil (to block thyroid hormone synthesis via the Wolff-Chaikoff effect).
 - Prednisolone** (glucocorticoids)
 - Diltiazem** for tachycardia, if not controlled by propranolol alone.

EXTRA EDGE

- Before the availability of beta blockers**, drugs that deplete catecholamine stores such as *reserpine* and *guanethidine* were used.

PARATHYROID GLAND

- Parathormone (PTH)** secreted by *chief cells* of *parathyroid*—major hormone in *serum calcium homeostasis*.

Functions of PTH:

- ↑ bone reabsorption by osteoclasts = ↑ *serum calcium* levels
- ↑ kidney reabsorption of calcium in distal convoluted tubule
- ↓ *kidney reabsorption of phosphate*
- PTH induces conversion of 25-(OH) vitamin D to 1,25-(OH)₂ vitamin D by stimulating 1-α-hydroxylase in kidney → 1,25-(OH)₂ vitamin D → ↑ *intestinal reabsorption of calcium and phosphate*. ("PTH = *Phosphate reTaking Hormone!!*").

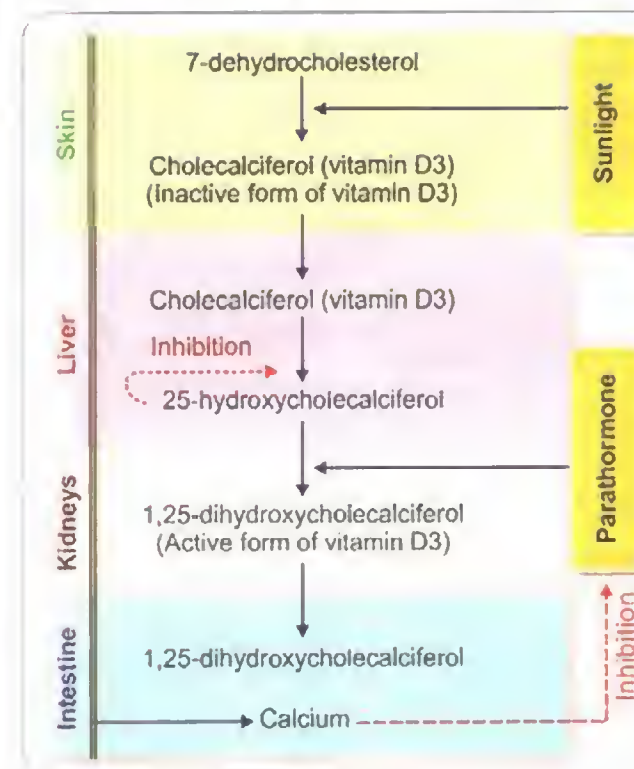


Fig. 21.80: Schematic diagram showing activation of vitamin D

Calcitonin

- Calcitonin is produced by *parafollicular C cells* of the *thyroid*.
- Hypocalcemic hormone** (antagonist to PTH):
 - It ↓ *bone resorption by osteoclasts*; hence *human calcitonin* is used in *Paget's disease*; calcitonin nasal spray used in *postmenopausal osteoporosis*.
 - It ↓ proximal tubular calcium and phosphate reabsorption by direct action on kidney (very minor role in calcium homeostasis).
- Parathyroid, thymus, and cells of medullary carcinoma of thyroid** also contain calcitonin.

Hyperparathyroidism

Type and definition	Cause	Serum calcium	PTH
Primary (autonomous secretion of PTH)	Single adenoma (MC cause in 90%)	↑	Not suppressed
Secondary (↑ PTH secretion to compensate for prolonged hypocalcemia and is a/w hyperplasia of all parathyroid tissue; its effect is to restore serum calcium levels at the expense of calcium stores in bone)	Chronic renal failure (MC cause) Malabsorption Osteomalacia and rickets	↓	↑
Tertiary (in some cases of Sec. Hyperparathyroidism continuous stimulation of parathyroids results in adenoma formation and autonomous PTH secretion)		↑	Not suppressed

Clinical Features of Hyperparathyroidism

- The classic quartet of '*stones, bones, abdominal groans and psychic moans*'!
 - Stones** = renal stones
 - Bones** = severe bone disease
 - Abdominal groans** = pancreatitis and
 - Psychic moans** = psychiatric disorder.
- At present surgery is the only curative option for *primary hyperparathyroidism*.
- Bone manifestations of secondary hyperparathyroidism** In *Chronic renal failure* (CKD) patients starts at GFR < 60 mL/min/1.73 m².
- Classic bone lesion of secondary hyperparathyroidism is—von Recklinghausen's disease of bone or *osteitis fibrosa cystica* (can also occur in primary hyperparathyroidism but rare these days due to earlier detection of disease).
- Calciophylaxis** (calcific uremic arteriolopathy) is the end stage of secondary hyperparathyroidism with arteriolar occlusion resulting in cutaneous ulceration and gangrene.
- Cinacalcet** sensitizes calcium sensing receptor (CASR) in parathyroid gland to circulating PTH—decreases PTH - used in primary and secondary hyperparathyroidism.

Radiology of hyperparathyroidism

- ▶ **Subperiosteal resorption** of phalanges (particularly radial side of middle phalanx of middle finger).
- ▶ **Loss of lamina dura** of tooth.
- ▶ **Brown's tumor** (an X-ray manifestation of *Osteitis fibrosa cystica*) is an expansile lytic lesion, which appears like a bone tumor, generally afflicting the **maxilla/mandible**.
- ▶ **'Pepper pot' appearance** of the skull.
- ▶ **'Rotting fence post' appearance** of proximal femur.

Indications for Parathyroidectomy in Primary Hyperparathyroidism

- Urinary tract calculi
- Reduced bone density
- High serum calcium
- All in younger age group <50 years
- Deteriorating renal function
- Symptomatic hypercalcemia.

EXTRA EDGE

- Increased osteoclastic bone resorption occurs and a/w Brown tumors as mentioned in above box.

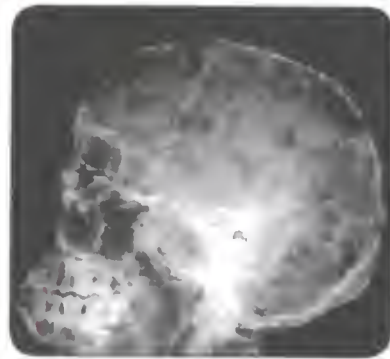


Fig. 21.81: Plain X-ray skull. Note the characteristic salt-pepper appearance of the skull bone



Figs. 21.82A and B: X-ray of humerus bone and hand bones showing bone features—brown tumor—osteitis fibrosa cystica

Hypoparathyroidism

- **MC seen following thyroidectomy** (damage to parathyroids or their blood supply)
- Can also be caused by *DiGeorge syndrome*, *Wilson syndrome* and *autoimmune polyglandular syndrome*
- Children: **tetany, carpopedal spasms, stridor** and convulsions
- **Adults:** tingling of lips/hands, abdominal cramps
- Chvostek's sign: tapping facial nerve in front of the ear causes twitching of facial muscles
- Trousseau's sign: inflation of BP cuff on the upper arm to more than systolic BP is followed by carpal spasm within 3 minutes
- **Prolonged QT interval, papilledema, cataracts, basal ganglia calcification** may also occur.

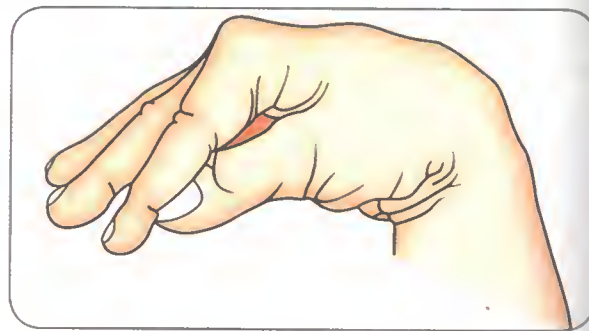


Fig. 21.83: Carpopedal spasm

Pseudo-Hypoparathyroidism

- **Tissue resistance** to effects of PTH (kidney unresponsive to PTH); **PTH levels are markedly elevated**
- PTH receptor is normal but there are defective post receptor mechanisms
- Clinically: **short stature, short 4th metacarpals and metatarsals, rounded face, obesity and subcutaneous calcification—Albright hereditary osteodystrophy.**

Pseudo-Pseudo-Hypoparathyroidism

- Above clinical features BUT **serum calcium and PTH concentrations are normal.**
- Inheritance of gene defect from a father with pseudo hypoparathyroidism results in pseudo-pseudo hypoparathyroidism (**gene imprinting**).

ADRENAL GLAND

Development of Adrenal Gland

- Adrenal cortex : from mesoderm
- Adrenal Medulla : from Neural Crest ("MNC = Multi National Company!!")

Primary regulatory control	Anatomy	Secretory products
Renin-Angiotensin →	Zona Glomerulosa	→ Aldosterone (mineralocorticoids)
ACTH, hypothalamic CRH →	Zona Fasciculata	→ Cortisol (glucocorticoids)
ACTH, hypothalamic CRH →	Zona Reticularis	→ Sex hormones (Adrenocorticoids)
Preganglionic sympathetic fibers →	Medulla	→ Catecholamines (epinephrine, norepinephrine)

EXTRA EDGE

- The weight of a normal adrenal gland is approximately 4 g.
- The adrenal glands are situated near the upper poles of the kidneys, in the retroperitoneum, within Gerota's capsule.

Arterial Supply of Adrenals

- Superior suprarenal A, a branch of *inferior phrenic A*
- Middle suprarenal A, a branch of *abdominal aorta*
- Inferior suprarenal A, a branch of *renal A*.

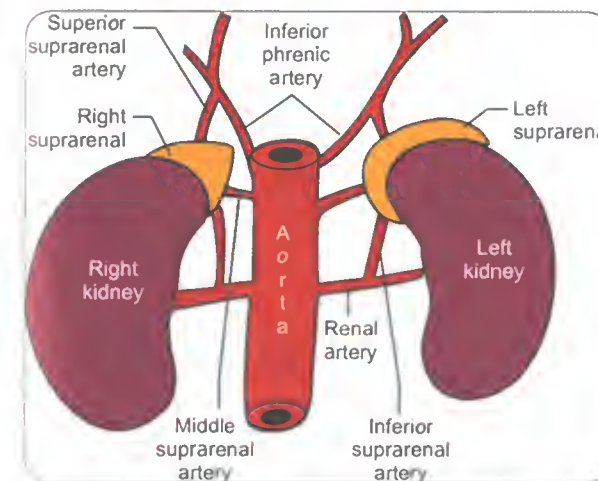


Fig. 21.84: Arterial supply of suprarenal glands

Venous Drainage

- Right suprarenal V → Inferior vena cava
- Left suprarenal V → left renal vein.
- (Same venous drainage as in right and left gonadal (testis/ovary) veins!).

Synthesis of Aldosterone

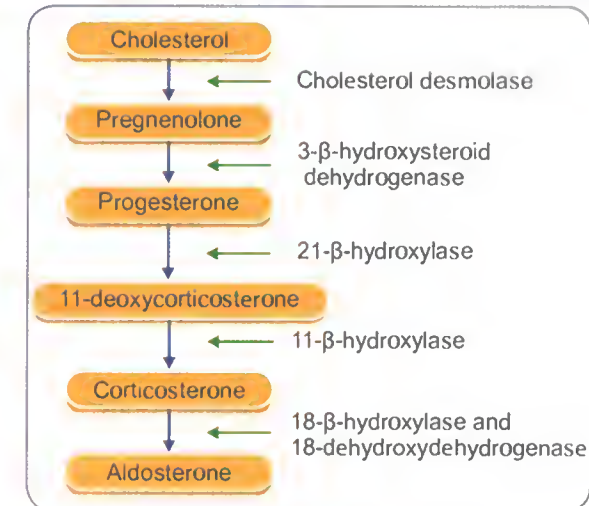


Fig. 21.85: Synthesis of aldosterone

Hyperaldosteronism

Primary (Conn's syndrome)	Secondary
<ul style="list-style-type: none"> • MC cause is • MC Caused by aldosterone secreting tumor (unilateral adrenocortical adenoma) resulting in HTN, hypokalemia, metabolic alkalosis and low plasma renin • The plasma aldosterone/renin ratio is the most reliable test for screening for primary aldosteronism 	<ul style="list-style-type: none"> • Due to extra-adrenal cause – renal artery stenosis, CRF, CHF, cirrhosis, or nephrotic syndrome. • Kidney perception of low intravascular volume results in an overactive renin-angiotensin system – hence it is a/w high plasma renin

Regulation of Aldosterone Secretion (See Fig. 21.86) Liddle and GoRdon syndrome

Pseudohyperaldosteronism	
Liddle syndrome (Type 1) <ul style="list-style-type: none"> • HTN + Low plasma aldosterone and Low renin + hypokalemia + metabolic alkalosis • Mutations of epithelial sodium channel • Autosomal dominant • Treatment: Amiloride 	GoRdon syndrome (Type 2) <ul style="list-style-type: none"> • HTN + Low plasma renin + hyperkalemia + metabolic acidosis • Mutations of WNK kinases 1 to 4 • Autosomal dominant • Treatment: Thiazides

Synthesis of Cortisol

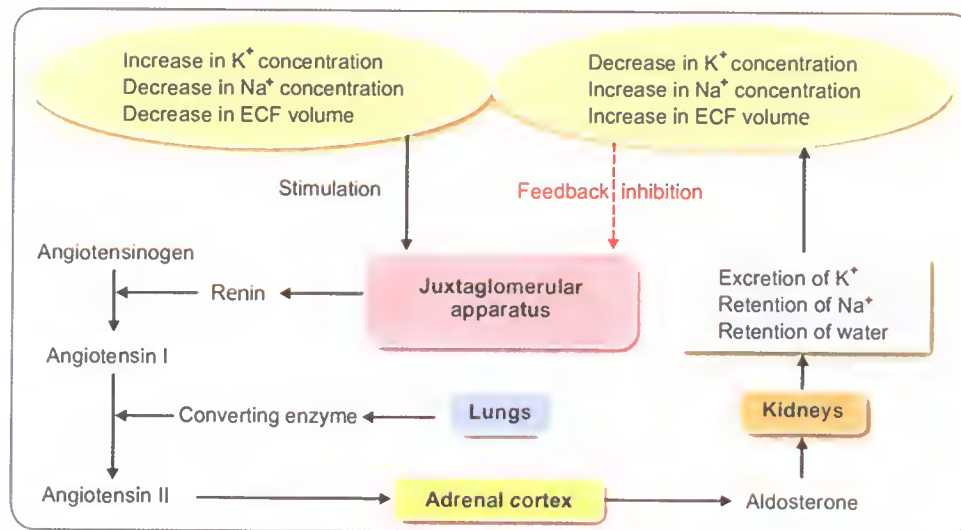


Fig. 21.86: Regulation of aldosterone secretion

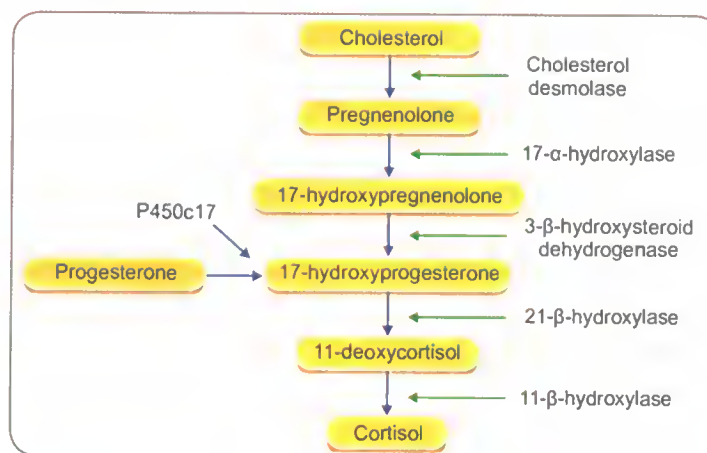


Fig. 21.87: Synthesis of cortisol

Cushing's Syndrome

- ↑ glucocorticoids due to various causes such as

↓ ACTH	↑ ACTH
<ul style="list-style-type: none"> Iatrogenic (chronic steroid use); – MC cause of Cushing's "syndrome" Primary adrenal (hyperplasia/neoplasia) 	<ul style="list-style-type: none"> Cushing's "disease" (primary pituitary adenoma) Ectopic ACTH production (small cell lung Ca)

Clinically:

- **C:** Central Obesity, Collagen fiber weakness (purple skin striae), Comedones (acne), Cataracts (posterior subcapsular)
- **U:** Urinary free cortisol and glucose increase

- Suppressed immunity, supraclavicular fats pads and buffalo hump on neck
- **H:** HTN, hyperglycemia (insulin resistance), Hypercholesterolemia, Hypokalemic alkalosis, Hollow bones (osteoporosis)
- **I:** Iatrogenic ("Cushing syndrome")
- **N:** Noniatrogenic ("Cushing disease" due to Neoplasms), No menses (amenorrhea), moon facies, myopathy (proximal);
- **G:** Glucose intolerance, Growth retardation
- **Dexamethasone suppression test:**
 - **Healthy:** ↓ cortisol after low dose
 - **ACTH producing pituitary adenoma:** ↑ cortisol after low dose, ↓ cortisol after high dose
 - **Ectopic ACTH producing tumor** (small cell lung Ca): ↑ cortisol after **low and high dose**.

EXTRA EDGE

- **Low dose** dexamethasone suppression test is for differentiating **hypercortisolism from normality**
- **High dose** dexamethasone (8 mg) suppression test is for differentiating between ACTH producing **pituitary tumor** and **Ectopic** ACTH production.
- **Nelson syndrome:** enlargement of existing ACT secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease (due to removal or cortisol feedback mechanism); presents with hyperpigmentation, headaches and bitemporal hemianopia; treat with pituitary irradiation or surgical resection.

Pseudo-Cushing's Syndrome

- A condition in which patients display the signs, symptoms, and abnormal hormone levels seen in Cushing's syndrome. It is an idiopathic condition.
- **Causes of pseudo-Cushing's syndrome:**
 - Obesity
 - Chronic alcoholism
 - Depression
 - Acute illness of any type.

Addison's disease

- **Addison disease = Primary adrenal insufficiency** due to adrenal cortex atrophy by destruction or disease.
- Symptoms are evident only when **90% of adrenal cortex is destroyed**.
- **Etiology:**
 - "Idiopathic" atrophy (autoimmune, adrenoleukodystrophy)
 - Surgical removal
 - Infection (TB, fungal, viral—especially in AIDS patients).

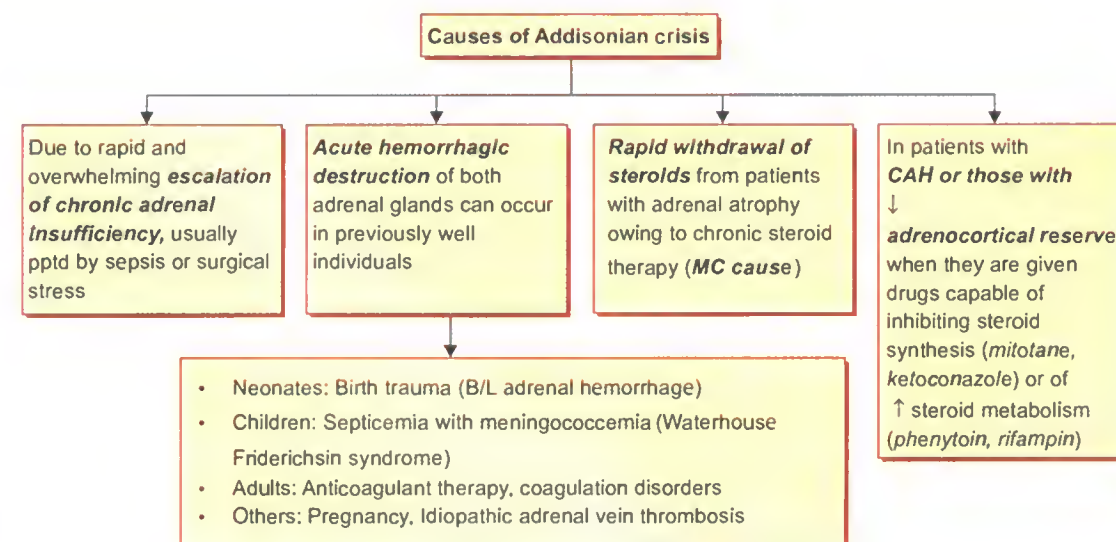
- **Clinically:**
 - **Hypotension** (**hyponatremic** volume contraction)
 - **Skin hyperpigmentation** (due to **MSH**, a by-product of ↑ ACTH production)
 - **Hyperkalemia; Hypoglycemia**
 - **Dehydration** and salt craving.
- **Treatment:** Glucocorticoids and mineralocorticoids.

Addisonian Crisis

- **Addisonian crisis** (adrenal crisis) = **Acute adrenal insufficiency** with severe **hypotension and shock** (see Flowchart)
- **Clinically:** fever, nausea, vomiting, severe abdominal pain, hypotension, hypovolemic vascular collapse – often mistaken for "acute abdomen".
- **Treatment:** Treat primary cause, replacement glucocorticoids; with large doses of steroid, i.e., 100–200 mg hydrocortisone, the patient receives a maximal mineralocorticoid effect, and supplementary mineralocorticoid is superfluous.
- **Lab Features:** **Hyponatremia; Hyperkalemia; Hypoglycemia** and **hypercalcemia**; ↓ Cl⁻ and HCO₃⁻

Incidentaloma

- **Incidentaloma** is an adrenal mass, detected incidentally by imaging studies conducted for other reasons, not known previously to have been present or causing symptoms.
- **MC incidentaloma (75%) is nonfunctioning adenomas.**
- The main goal is to **exclude** a functioning or malignant adrenal tumor.



- **NEVER biopsy** an adrenal mass until *pheochromocytoma* has been biochemically excluded.
- The **ONLY** indication for adrenal gland biopsy is to **confirm adrenal gland metastasis**.
- Any nonfunctioning adrenal tumor > **4 cm in diameter** and smaller tumors that increase in size over time should undergo **surgical resection**.

Pheochromocytoma

- MC tumor of **adrenal medulla** in adults.
- Derived from **chromaffin cells** (derived from **neural crest**).
- **MC extra-adrenal site** is in the superior para-aortic region between the diaphragm and lower renal poles; the organ of Zuckerkandl is also a **common extra-adrenal site**.
- Tumors secrete *epinephrine, NE and dopamine (catecholamines)*.
- ↑↑ Urinary **VMA**, ↑↑ plasma and urinary catecholamine levels.
- Tumor syndromes a/w pheochromocytoma: **MEN II and MEN III**; VHL syndrome; NF-1; Familial paraganglioma syndrome.
- Clinical features (**episodic/spells of hyperadrenergic symptoms**) – **5P's**
 - Pressure (Hypertension, *episodic* fluctuations)
 - Pain (headache)
 - Perspiration (sweating)
 - Palpitation (tachycardia, anxiety, tremors)
 - Pallor.
- MRI is preferred because contrast media used for CT scans can provoke paroxysms. Classically, pheochromocytomas show a **'Swiss cheese'** configuration.
- **I¹²³-MIBG scan** (*metaiodobenzylguanidine*) is a nuclear isotope scan to detect occult collections of metastatic pheochromocytoma.
- Cut surface of pheochromocytoma is **greyish pink**.
- Pathology signs of malignant pheochromocytoma: An **increased PASS** (pheochromocytoma of the adrenal gland scale score), a high number of **Ki-67-positive** cells, **vascular invasion** or a **breached capsule**.
- **Treatment:**
 - Treat with **phenoxybenzamine**, (irreversible **α-blocker**), to first control **BP** (i.e. to avoid consequences of catecholamine excess during surgery); ALSO without α-blockade BP can drop significantly postoperatively.
 - A dose of 20 mg of phenoxybenzamine initially should be increased daily by 10 mg until a daily dose of 100–160 mg is achieved and the patient reports symptomatic postural hypotension.

- Additional β-blockade is required if tachycardia or arrhythmias develop; this should not be introduced until the patient is α-blocked (i.e, Propranolol is used **after** the α-blocker).
- **Laparoscopic resection** is now routine in the treatment of pheochromocytoma.

Rule of 10s for pheochromocytoma

- **10%** malignant
- **10%** bilateral
- **10%** extra-adrenal
- **10%** calcify
- **10%** in kids
- **10%** familial/inherited

Adrenal Metastases

- Adrenal metastases are discovered at autopsy in **one-third** of patients with **malignant disease** (less frequently during life).
- Adrenal metastases are **MC** due to **Ca breast**.

Adrenocortical Carcinoma

- Very rare tumor; MC presentation—cortisol excess (Cushing's syndrome).
- The WHO classification is based on the **McFarlane classification** and defines four stages: tumors <5 cm (stage I) or >5 cm (stage II), locally invasive tumors (III) or tumours with distant metastases (IV).
- Complete **tumor resection** (R0) is associated with favorable survival and should be attempted whenever possible.

Differences between Adrenal Adenoma and Adrenal Malignancy on Imaging

	Adrenal adenoma	Adrenal malignancy (primary carcinoma, pheochromocytoma or metastases)
Size	< 2.5 cm	> 4.0 cm
Growth	No growth usually for 6 months	Grows rapidly
CT scan – Plain	Low density (< 10 HU) or Low attenuation due to intracellular fat	High density (> 20 HU)
CT scan – IV contrast enhanced	Enhance little More Rapid Washout	Enhance more Less Rapid Washout
Chemical shift MRI	Signal dropout on out of phase imaging	No signal difference on in/out of phase imaging (due to less intracellular fat)
PET	No uptake of FDG (18-fluoro-2-deoxyglucose)	Increased FDG uptake

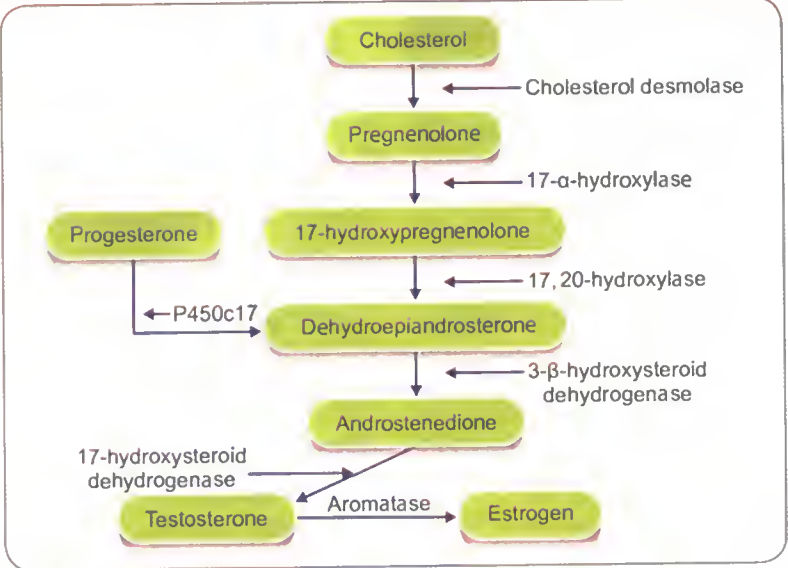


Fig. 21.88: Synthesis of adrenal sex hormones

DIABETES MELLITUS

Comparison of Two Types of Diabetes Mellitus

	Type 1 (earlier called IDDM)	Type 2 (earlier called NIDDM)
Age at onset	Childhood or puberty, < 30 years	Usually > 40 years
A/w HLA	Yes, HLA DR-3 and DR-4	No
Genetic predisposition	Weak, polygenic	Strong polygenic
Cause	Autoimmune destruction of b-cells leading to failure of pancreas to secrete insulin; occurs in patients with genetically susceptible HLA locus and MC triggered by viral infection	Insulin resistance in tissues and inadequate insulin secretion by the pancreas to compensate
Islet cell pathology	Insulinitis (B cells destroyed); islet leukocytic infiltrate	Normal number of B cells, but with islet amyloid polypeptide (IAPP) deposits
Body type	Thin	Obese
Incidence	15%	85%
Onset of symptoms	Rapid	Gradual

Contd...

Contd...

	Type 1 (earlier called IDDM)	Type 2 (earlier called NIDDM)
Development of ketoacidosis	Common	Rare
Acute complications	Ketoacidosis	Hyperosmolar hyperglycemic nonketotic coma
Serum insulin	Low	Increased or normal
Serum C-peptide	↓; can be normal during the honeymoon period	↓ late in the disease
Treatment	Insulin	Oral hypoglycemic agents; possibly insulin

MODY

- Maturity-onset diabetes of the young (**MODY**) is a subtype of DM characterized by:
 - **monogenic—autosomal dominant** inheritance
 - early onset hyperglycemia (usually <25 years), and
 - impairment in insulin secretion.
- 6 types of MODY are described - **type 3 MODY** is MC (due to mutations in **hepatic nuclear factor 1-alpha**).

Flatbush diabetes

- Named after the area "Flatbush" in New York where it was discovered first.
- A.k.a **idiopathic type 1 diabetes**. MC seen in **African-Americans**.
- Present with **very high blood glucose** levels and **diabetic ketoacidosis**.
- **NO** autoimmune markers present.
- **Obesity** and **high BMI** present.
- Initially require **insulin BUT** later become euglycemic with oral hypoglycemic agents.
- Etiology: Unknown

EXTRA EDGE

- **Latent Autoimmune Diabetes of Adults (LADA):**
 - A.k.a "**1.5 diabetes**" (since it has some features of type 1 and some of type 2!)
 - **Adult age** at diagnosis; symptoms develop much slower than in juvenile diabetes.
 - Diabetes associated auto-antibodies (**GAD** - Glutamic Acid Decarboxylase antibodies) are present.
 - **NO** family h/o diabetes.
 - **BMI < 19**; High opening sugars; **inadequate response** to oral hypoglycemic agents.
 - May ultimately become insulin dependent.

Diabetes due to Genetic Defects in Insulin Action

- Type A insulin resistance
- Leprechaunism
- Rabson-Mendenhall syndrome
- Lipoatrophic diabetes.

Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)
- Hemoglobin A1c $\geq 6.5\%$
- **2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL)** during an oral glucose tolerance test (2h after consumption of 75 g glucose in water).

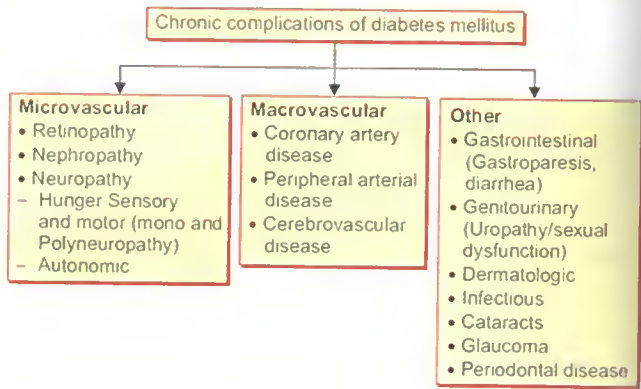
Diabetic Ketoacidosis

- Most important complication of **type 1 DM**; maybe the initial manifestation
- **Pathophysiology:** Usually due to \uparrow in insulin requirement from \uparrow in stress (e.g. infection). Excess fat breakdown and \uparrow ketogenesis from the \uparrow in free fatty acids, which are then made into ketone bodies (b-hydroxybutyrate > acetoacetate) \rightarrow life-threatening **metabolic acidosis**.

- Clinically: **Delirium/psychosis**, **Dehydration** **Kussmaul's respiration** (rapid/deep breathing), **Ketonic (Fruity) breath odor** (due to exhaled acetone) **Abdominal pain**, and **nausea/vomiting**. (**DKA!**)
- Labs: **hyperglycemia**, \uparrow **blood ketone bodies**, \uparrow **anion gap metabolic acidosis**, **hyperkalemia**, but depleted intracellular potassium due to transcellular shift from \downarrow insulin.
- Treatment: **IV fluids**, **insulin**, **KCl** (to replete intracellular stores), **sodium bicarbonate**, **glucose**.
- Complications: **mucormycosis**, cerebral edema, cardiac arrhythmias, heart failure.

Hyperosmolar (Nonketotic Hyperglycemic) Coma

- Commonly seen in persons with **type 2 DM**.
- **Relative insulin deficiency and inadequate fluid intake** are the underlying causes of HHS.
- Clinically: profound **dehydration** and **hyperosmolality**, hypotension, tachycardia, and altered mental status.
- **Notably absent** are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA.
- Precipitating factors: myocardial infarction or stroke or infections.
- Labs: **marked hyperglycemia** [plasma glucose may be >55.5 mmol/L (1000 mg/dL)], **hyperosmolality** (>350 mosmol/L), and **prerenal azotemia**.
- In contrast to DKA, **acidosis and ketonemia are absent or mild**.
- Treatment: same as for DKA, except that **faster fluid replacement is to be instituted** and **alkali is usually not required**.
- These patients are **usually relatively sensitive to insulin** and **approximately half the dose of insulin recommended for the treatment of DKA should be employed**.
- These patients are more prone to thrombosis, **prophylactic heparin** may be required.



Somogyi Effect

- The Somogyi effect is the **body's response to hypoglycemia**. If too much insulin is given at dinner time, the glucose level at 3 AM on the next morning will be low (hypoglycemia). The body reacts to hypoglycemia by releasing stress hormones, which cause a high glucose level at 7 AM. The treatment is to **decrease** evening insulin.

Dawn Phenomenon

- The Dawn phenomenon is **hyperglycemia caused by normal secretion of growth hormone early in the morning**. The glucose level is high at 7 AM and normal or high at 3 AM (no hypoglycemia). The treatment is to **increase** evening insulin.

HYPOGLYCEMIA

- Hypoglycemia is most convincingly documented by Whipple's triad:
 - Symptoms consistent with hypoglycemia,
 - A low plasma glucose concentration measured with a precise method (not a glucose monitor), and
 - Relief of symptoms after the plasma glucose level is raised.

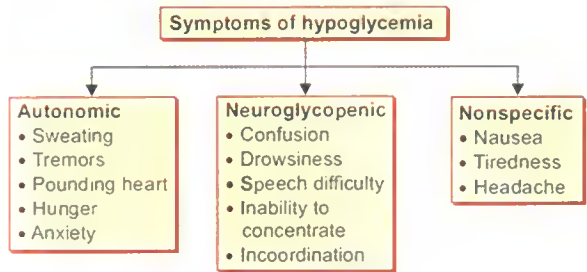
Causes of Hypoglycemia in Adults

Ill or Medicated Individual

- Drugs (Insulin or insulin secretagogue, Alcohol)
- Critical illness (Hepatic, renal or cardiac failure Sepsis, Inanition)
- Hormone deficiency (Cortisone, Glucagon and epinephrine (in insulin-deficient diabetes)
- Non-islet cell tumor

Seemingly Well Individual

- Endogenous hyperinsulinism:
 - Insulinoma
 - Functional β -cell disorders (nesidioblastosis)
 - Noninsulinoma pancreatogenous hypoglycemia
 - Postgastric bypass hypoglycemia Insulin autoimmune hypoglycemia
 - Antibody to insulin
 - Antibody to insulin receptor Insulin secretagogue
 - Other.



Multiple Endocrine Neoplasia (MEN) Syndromes

MEN 1 (Wermer's syn.) - 3Ps!	Parathyroid adenoma, Pancreatic neuroendocrine islet cell tumor - a/w Zollinger-Ellison syn; insulinoma, VIPoma Pituitary adenoma (anterior pituitary tumors) Carcinoid	AD, a/w mutation of MEN1 (menin, a tumor suppressor gene on chromosome 11)
MEN 2A (Sipple syn.) - 2Ps!	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia (hyperparathyroidism)	AD, monitor calcitonin and calcium levels; a/w RET mutation
MEN 2B (MEN 3) - 1P!	Medullary thyroid carcinoma, Pheochromocytoma Mucosal neuroma Marfanoid habitus	

EXTRA EDGE

- All MEN syndromes are autosomal dominant—"All MEN are dominant!!"

Autoimmune Polyendocrine Syndromes (APS)

- Autoimmunity is caused by the breakdown of mechanisms that maintain immune tolerance to self tissues. Most self-reactive T cells are deleted in the thymus, resulting in central tolerance.
- The **autoimmune regulator (AIRE)** protein has been found to be important for the maintenance of self tolerance. **Mutations** in the **AIRE gene** cause **Autoimmune Polyendocrine Syndrome**.
- **APS-1:**
 - A.k.a **APECED** (Autoimmune-Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy)
 - AR; mutations in **AIRE** (autoimmune regulator) **gene**.
- **APS-2:**
 - A.k.a **Schmidt's syndrome**;
 - AD; a/w HLA-DR3 and CTLA-4;
 - APS-2 is more common.

Function of the Endocrine Pancreas

- The endocrine cells of the pancreas are grouped in the **islets of Langerhans**, which constitute approximately 1-2 percent of the mass of the pancreas (1-1.5 gram)
- There are about **one million islets** in a healthy adult human pancreas
- There are four main types of cell in the Islets of Langerhans, which can be classified according to their secretions:
 - **Beta cells** producing **insulin** (65-80 percent of the islet cells);
 - **Alpha cells** producing **glucagon** (15-20 percent);

- **Delta** cells producing **somatostatin** (3–10 percent);
- **Pancreatic polypeptide** (PP) cells containing polypeptide (1 percent).

INSULINOMA

- **MC** pancreatic neuroendocrine tumor.
- It is an insulin-producing tumor of the pancreas causing the clinical scenario known as **Whipple's triad**, i.e. symptoms of hypoglycaemia after fasting or exercise, plasma glucose levels <2.8 mmol/L and relief of symptoms on intravenous administration of glucose.
- Approximately **ONLY 10 percent are malignant** (BUT remember - all other PNETs have a 50% chance of being malignant!).
- The diagnosis of insulinoma requires the demonstration of an **elevated plasma insulin level at the time of hypoglycemia**.
- The most reliable test to diagnose insulinoma is a **fast up to 72 h** with serum glucose, C-peptide, proinsulin, and insulin measurements every 4–8 h.
- **Arteriography** was previously considered to be the **gold standard** for the diagnosis of insulinoma BUT now **endoscopic ultrasound** is the investigation of choice.
- For all other PNETs - **somatostatin receptor scintigraphy (SRS)** is the **inv of choice**.
- **Surgical resection** is the treatment of choice.

OTHER PNET'S

Tumor	Comments
Gastrinoma	Intractable or recurrent peptic ulcer disease (hemorrhage, perforation), complications of peptic ulcer, diarrhea (see under GIT chapter for more on gastrinoma)
Nonfunctional tumours	Obstructive jaundice, pancreatitis, epigastric pain, duodenal obstruction, weight loss, fatigue
Vipoma	Profuse watery diarrhea , hypotension, abdominal pain
Glucagonoma	Migratory necrolytic erythema , glossitis, stomatitis, angular cheilitis, diabetes, severe weight loss, diarrhea
Somatostatinoma	Cholelithiasis, diarrhea, neurofibromatosis
Carcinoid	Flushing, sweating, diarrhea, edema (see under GIT chapter for more about carcinoids)

GENERAL MEDICINE**"Named Fevers"**

Break bone fever	Dengue
Gaol fever (epidemic typhus)	R. prowazekii
Haverhill fever	Streptobacillus moniliformis
Monkey fever	Kyasanur Forest Disease
Oraya fever (Carrion's disease)	Bartonella bacilliformis
Oriental spotted fever	R. japonica
Q fever	Coxiella burnetii
Relapsing fever	Borreliella recurrentis
Rocky mountain spotted fever	R. rickettsiae
Trench fever	R. quintana
Undulant fever, Malta fever	Brucella melitensis
Picket fence fever	Lateral sinus thrombophlebitis

Differences between Fever and Hyperthermia

Criteria	Fever	Hyperthermia
Occurrence	Common	Relatively rare
Clinically	Feeling cold, cold skin	Feeling hot, dry flushed skin
Temperature	Usually 38–41°C	May exceed 42°C
Main treatment	Antipyretics	Physical measures
Central regulation	Yes	No
Hypothalamic set point	Elevated	Normal
Mortality	Unusual	High (excluding minor forms such as dehydration)

Definition of hyperthermia: "An unchanged setting of the hypothalamic set point in conjunction with an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. Hyperthermia does NOT involve pyrogenic molecules".

Depression of consciousness level in **hypothermia** starts when the core body temperature falls **below 32°C**.

EXTRA EDGE

- **FUO (fever of Unknown Origin)** is now defined as:
 - Fever > 38.3°C (101°F) on at least two occasions
 - Illness duration of ≥ 3 weeks
 - No known immunocompromised state
 - Diagnosis that remains uncertain after a thorough history-taking, physical examination, and obligatory investigations.
- OLD Criteria REMOVED now is: "uncertain diagnosis despite 1 week of inpatient evaluation".

Quantifying Proteinuria

24 h urine protein	Significance
< 0.03 g	Normal
0.03–0.3 g	Microalbuminuria
0.3–0.5 g	Dipsticks positive
> 2.5 g	Likely glomerular disease
> 4.0 g	Nephrotic range – always glomerular

Pain Terminologies

Paresthesias:	Tingling or pins-and-needles sensations (excludes pain)
Dysesthesias:	All types of abnormal sensations including painful ones
Hypoesthesia:	Reduction of cutaneous sensation
Anesthesia:	A complete absence of skin sensation
Hypalgesia:	Reduced pain perception (nociception)
Analgesia:	Absent, pain perception (nociception)
Hyperesthesia:	Pain or increased sensitivity in response to touch
Allodynia:	A nonpainful stimulus, once perceived, is experienced as painful, even excruciating pain (e.g., elicitation of a painful sensation by application of a vibrating tuning fork)
Hyperalgesia:	Severe pain in response to a mildly noxious stimulus
Hyperpathia:	A broad term, encompasses all the phenomena described by hyperesthesia, allodynia, and hyperalgesia
Graphesthesia:	The capacity to recognize with eyes closed letters or numbers drawn by the examiner's fingertip on the palm of the hand

Contd...

Contd...

Synesthesia

is a neurological condition in which stimulation of one sensory or cognitive pathway leads to automatic, involuntary experiences in a second sensory or cognitive pathway

Stereognosis:

Refers to the ability to identify common objects by palpation, recognizing their shape, texture, and size

Body Mass Index (Quetelet's index)

BMI	Classification
18.5–24.9	Normal range
25.0–29.9	Overweight
> 30	Obese
30.0–34.9	Class I
35.0–39.9	Class II
> 40.0	Class III

BMI in Children

Weight status category	Percentile range
Underweight	Less than the 5th percentile
Healthy weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese	Equal to or greater than the 95th percentile

EXTRA EDGE

- BMI = Weight (kg) / Height² (m)
- Corpulence index = Actual weight / Desired weight (should not exceed 1.2) - It is a "height INDEPENDENT" index.
- Broca Index = Height (cm) - 100.

Basal Metabolic Rate (BMR)

- BMR refers to the energy that is expended by the body at rest, but not while asleep.
- It indicates the amount of energy that is required to keep the body alive and is strongly proportional to lean body mass which is the amount of metabolically active tissue.
- This emphasizes the fact that even resting muscle is metabolically active.

Kyasanur Forest Disease (KFD)

- KFD is a *tick borne, viral hemorrhagic fever* found in **Karnataka, India and western Siberia**.
- Named after Kyasanur forest area in **Shimoga district, Karnataka** where cases were first reported.
- KFD is seen in monkeys and humans and is genetically related to RSSE (Russian spring summer encephalitis)
- **Reservoir hosts: rats and squirrels** (birds, bats are less important - Park/23rd)
- **Amplifier hosts: monkeys**
- **Vector tick: *H. spinigera* (hard tick)**
- Major outbreak: in 1982 in Belthangady taluk, South Canara, 1142 human cases were reported with 104 deaths
- Russian counterpart of KFD is *Omsk hemorrhagic fever*.

Soft ticks transmit	Hard ticks transmit
<ul style="list-style-type: none">• Q fever• Relapsing fever	<ul style="list-style-type: none">• Tick typhus• Viral encephalitis• Viral hemorrhagic fevers• Tularemia• Tick paralysis• Human babesiosis• KFD

Pseudo's—You Should Know

- Pseudo hemoptysis—Serratia pneumonia (also red diapers syndrome)
- Pseudo paralysis—Vitamin C deficiency
- Pseudo fractures—Osteomalacia
- Pseudo dementia—Depression
- Pseudo community—Paranoid states
- Pseudo lymphoma—Sjögren's syndrome
- Pseudo tabes—Diabetic foot
- Pseudo coxalgia—Perthe's disease.

- **Normal** area of the mitral valve orifice = 4–6 cm² (in normal adults)
- **Significant** obstruction = orifice area is reduced to < ~2 cm²
- **"Severe"** stenosis = orifice area is reduced to < 1 cm²

EXTRA EDGE

- **DASH** = Dietary Approaches to Stop Hypertension.
- DASH diet is a lifelong approach to healthy eating to help treat/prevent high hypertension. The DASH diet encourages you to reduce the sodium in the diet.
- **Standard DASH** diet (can consume up to 2,300 mg of sodium/day).
- **Lower sodium DASH** diet (can consume up to 1,500 mg of sodium/day).

Markers of Risk for Coronary Artery Disease

- hs CRP (high-sensitivity CRP – *best characterized* inflammatory marker)
- Lp(a)
- Fibrinogen
- PAI-1
- Myeloperoxidase
- Lipoprotein-associated phospholipase A2Size fractions of LDL particles
- Concentrations of homocysteine
- Interleukin-6
- CD-40 ligand
- Placental growth factor.

Copper

- **Copper** is a *cofactor* for *lysyl oxidase*, the enzyme that forms cross-links between *collagen* in connective tissue.
- **Dietary sources of copper** include shellfish, liver, nuts, legumes, bran, and organ meats.
- Copper is also a component of *fetoprotein*, a transport protein involved in the basolateral transfer of iron during absorption from the enterocyte.

Copper is an integral part of numerous enzyme systems including	Copper plays a role in
<ul style="list-style-type: none">• Amine oxidases• Ferroxidase (ceruloplasmin)• Cytochrome-c oxidase• Superoxide dismutase, and• Dopamine hydroxylase	<ul style="list-style-type: none">• Iron metabolism• Melanin synthesis• Energy production• Neurotransmitter synthesis and CNS function• Synthesis and cross-linking of elastin and collagen• Scavenging of superoxide radicals

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following conditions:

1. **Fever** (oral temperature >38°C) or **hypothermia** (<36°C);
2. **Tachypnea** (>24 breaths/min);
3. **Tachycardia** (heart rate >90 beats/min);
4. **Leukocytosis** (>12,000/microL), **leucopenia** (<4,000/microL), or >10% bands.

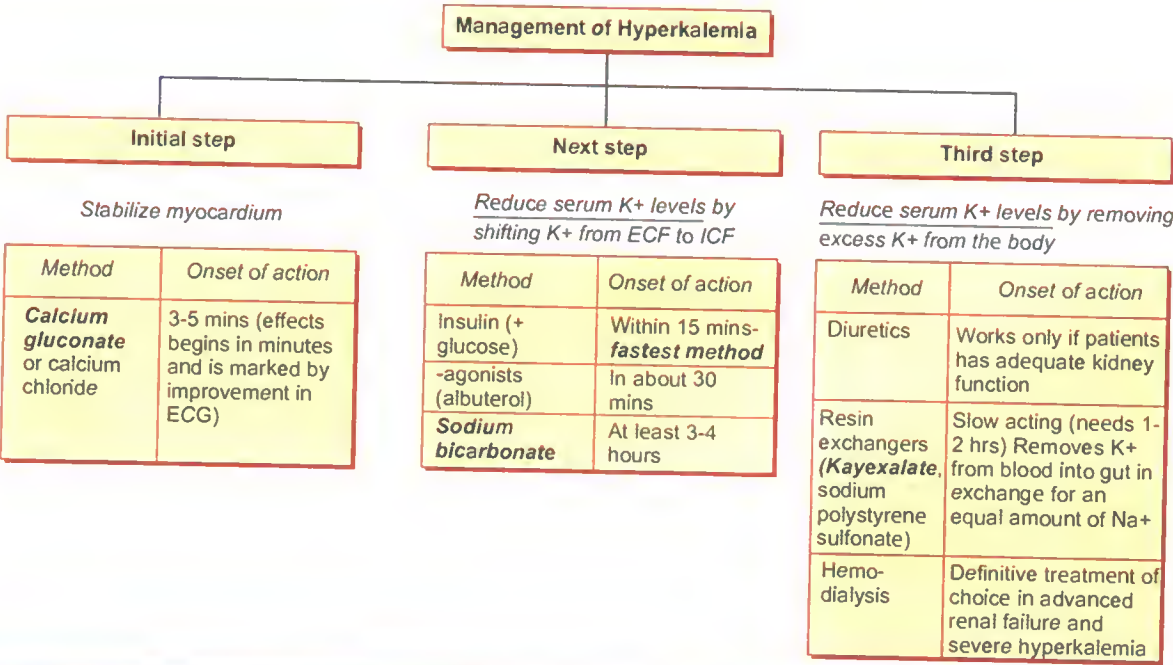
Other Definitions Used to Describe the Condition of Septic Patients

Bacteremia	Presence of bacteria in blood, as evidenced by positive blood cultures
Septicemia	Presence of microbes or their toxins in blood
Sepsis	SIRS that has a proven or suspected microbial etiology
Severe sepsis (similar to "sepsis syndrome")	Sepsis with one or more signs of organ dysfunction—hypotension, oliguria, thrombocytopenia etc.
Septic Shock	Sepsis with hypotension (arterial BP <90 mmHg systolic, or 40 mmHg less than patient's normal BP) for at least 1 h despite adequate fluid resuscitation; OR Need for vasopressors to maintain systolic BP ≥ 90 mmHg or mean arterial pressure ≥70 mmHg

Contd...

Refractory septic shock	Septic shock that lasts for >1 h and does not respond to fluid or pressor administration
Multiple-Organ Dysfunction Syndrome (MODS)	Dysfunction of more than one organ, requiring intervention to maintain homeostasis
<ul style="list-style-type: none">• International Staging System: for multiple myeloma relies on two factors, beta -2-microglobulin and albumin (Harrison's, 17th/704).• International Normalized ratio (INR): to assess anticoagulation due to reduction of vitamin K-dependent coagulation factors (2,7,9,10); it is commonly used in the evaluation of patients with liver disease. (Harrison's, 17th/734)• International Sensitivity Index (ISI) : the overall sensitivity of different thromboplastins to reduction of the vitamin K-dependent clotting factors II, VII, IX, and X in anticoagulated patients is now expressed as the ISI (Harrison's, 17th/368)	

Contd...



EPONYMOUS SIGNS

Sign	Associated conditions	Description
Aaron Sign	Appendicitis	Epigastric Pain With Pressure on Mcburney's Point
Abadie's Sign	Graves' Disease	Levator Palpebrae Superioris Spasm
Abadie's Symptom	Tabes Dorsalis	Absence of Pain on Achilles Tendon Pressure
Abderhalden Reaction	Pregnancy	Serum Reaction; Obsolete

Contd...

Contd...

Sign	Associated conditions	Description
Abelin Reaction	Syphilis	Presence of Arsenical Anti-Syphilitic; Obsolete
Addis Count	Pyelonephritis	Quantitative Cells And Casts In 24Hr. Urine
Adie Pupil	Ciliary Nerve Damage	Dilated Pupil, Poorly Reactive But With Normal Near Accommodation
Adson's Sign	Thoracic Outlet Syndrome	Obliteration of Radial Pulse With Manoeuvres
Alexander's Law	Vestibular Lesions	Describes Nystagmus In Vestibular Lesions
Allen's Test	Arterial Supply of The Hand	Tests For Presence of Palmar Ulnar-Radial Anastomosis (Palmar Arch)
Apgar Score		Assess Health of Newborn
Apley Grind Test	Meniscal Lesions	Manoeuvres To Elicit Knee Pain
Argyll Robertson Pupils	Neurosyphilis	Light-Near Dissociation
Arneth Count	Folate Deficiency	Lobulation of Neutrophil Nuclei
Asboe-Hansen Sign	Bullae	Extension of A Blister To Adjacent Unblistered Skin When Pressed
Aschheim-Zondek Test	Normal Pregnancy	Oestral Reaction In Mouse Injected With Pregnant Urine
Aschoff Body	Rheumatic Fever	Foci of Interstitial Inflammation In The Myocardium And Elsewhere
Ashby Technique	Hemolysis	Agglutination Test For Erythrocyte Survival
Auberger's Blood Group	Normal Physiology	Aua Antigen
Auenbrugger's Sign	Pericardial Effusion	Bulging Epigastrium
Auer Rods	Acute Myeloid Leukemia	Cytoplasmic Inclusions In Myeloblasts
Auspitz's Sign	Psoriasis	Punctate Bleeding When Scales Are Scraped
Austin Flint Murmur	Aortic Insufficiency	Mid-Diastolic Rumble Heard At Apex
Babinski Sign	Abnormal Plantar Reflex	Dorsiflexion of The Hallux With Fanning of The Remaining Phalanges Upon Soft Stimulation of The Lateral Plantar Surface of The Foot
Bainbridge Reflex	Normal Physiology	Increase In Heart Rate With Increase In Circulating Blood Volume
Balbani Rings	Rna Transcription	Large Chromosome Puff Indicating Site of Rna Transcription
Ballance's Sign	Abdominal/Splenic Trauma	Percussive Dullness Left Flank, Luq, Percussive Resonance Right Flank
Bancroft's Sign	Deep Vein Thrombosis	Pain on Anterior, But Not Lateral, Compression of Calf
Bárány Test	Vertigo, Vestibular Dysfunction	Nystagmus Elicited By Hot Or Cold Irrigation of Ear Canal
Barlow's Maneuver	Hip Dysplasia	Dislocation on Adduction of Hip
Bart Hemoglobin	Indicates A Specific Cause of Death In Some Stillborns	Loss of All Four Alpha-Globin Genes (Total Alpha-Thalassemia) Leads To Severely Anemic Stillborn Babies With Small Amounts of An Abnormal Hemoglobin Composed of Four Gamma Sub-Units (Bart's Hemoglobin)
Bastian-Bruns Sign	Spinal Cord Transection	Loss of Muscle Tone And Reflexes Below Lesion Level
Battle's Sign	Basal Skull Fracture	Mastoid Ecchymosis
Beau's Lines	Multiple, Including Trauma	Transverse Ridges on Nails
Beck's Triad	Cardiac Tamponade	Hypotension, Increased Central Venous Pressure (Jvp), Distant Heart Sounds
Becker's Sign	Thyrotoxicosis	Visible Pulsation of Retinal Arteries
Beevor's Sign	Spinal Trauma At T10, Als, Fsm�	Caudal Movement of Navel on Cervical Flexion
Bekhterev-Jacobsohn Reflex	Pyramidal Tract Lesions	Stroking Dorsal Radial Skin, With Forearm In Supination, Elicits Wrist And Finger Flexion

Contd...

Contd...

Sign	Associated conditions	Description
Bekhterev-Mendel Reflex	Pyramidal Tract Lesions	Toe Flexion on Percussion of Dorsum of Foot
Bence Jones Protein	Multiple Myeloma	
Benedict Solution	Diabetes Mellitus	Reagent For Presence of Monosaccharides
Berger Wave (Rhythm)	Normal Physiology	Electroencephalographic Alpha Wave
Bezold-Jarisch Reflex	Effect of Certain Alkaloids	Apnea, Bradycardia, Hypotension
Bielschowsky's Head Tilt Test	Lesions of Cranial nerve IV	Test For Palsy of Superior Oblique Muscle
Bing's Sign	Pyramidal Tract Lesions	Extension of The Great Toe on Pricking The Dorsum of The Foot With A Pin
Biot's Respiration	Brain Stem Herniation	Quick Shallow Respirations Followed By Period of Apnea
Bitot's Spots	Vitamin A Deficiency	Spots of Keratin Deposition In The Conjunctiva
Blumberg Sign	Peritonitis	Rebound Tenderness
Boas' Point	Gastric Ulcer	Dermal Hyperesthesia Just Left of T12
Boas' Sign	Acute Cholecystitis	Dermal Hyperesthesia At Inferior Angle of R Scapula
Bodansky Unit		Unit of Alkaline Phosphatase Concentration In Blood
Boston's Sign	Thyrotoxicosis	Spasmodic Ptosis on Downward Gaze
Bouchard's Nodes	Osteoarthritis	Bony Outgrowths on Dorsum of Proximal Interphalangeal Joints
Bracht-Wachter Bodies	Infective Endocarditis	Yellow-White Spots In The Myocardium
Branham's (Nicoladoni) Sign	AV fistula	Pressing on Proximal Portion of Av Fistula Results In Bradycardia
Braxton Hicks Contraction	Normal Pregnancy	"False Labor". Sporadic Contractions Beginning As Early As Mid 1st Trimester
Brewer Infarcts	Pyelonephritis	Dark Red Wedge Shaped Areas on Kidney Section Resembling Infarcts
Brissaud's Reflex	Pyramidal Tract Lesions	Plantar Stimulation Elicits Contraction of Tensor Fasciae Latae
Broadbent Inverted Sign	L Atrial Hypertrophy	Systole Palpable In Posterior Chest Wall
Broadbent Sign	Adhesive Pericarditis	Recession of L Inferior Intercostal Spaces
Broca Aphasia	Developmental Or Other Pathology of Various Frontal Cortical Areas	Expressive Aphasia
Brodie-Trendelenburg Percussion Test	Varicose Veins	Superficial Vein Is Percussed Proximally; If Impulse Is Felt Over Vein Distally, Valvular Incompetence Is Present
Brodie-Trendelenburg Test	Varicose Veins	Identifies Level of Valvular Incompetence
Brudziński Neck Sign	Meningitis	Neck Flexion Elicits Hip And Knee Flexion
Brudziński Cheek Sign	Meningitis	Pressure Beneath Zygoma Elicits Flexion of Forearm
Brudziński Symphyseal Sign	Meningitis	Pressure Over Symphysis Pubis Elicits Knee, Hip Flexion And Leg Abduction
Brudziński Reflex	Meningitis	Passive Flexion of Knee To Abdomen Elicits Flexion of Contralateral Hip And Knee
Bruit De Roger	Ventricular Septal Defect	Loud Pansystolic Murmur

Contd...

Contd...

Sign	Associated conditions	Description
Bruns Ataxia	Frontal Lobe Lesions	Difficulty Moving Feet In Contact With Floor, Tendency To Fall Backwards
Bruns Nystagmus	Cerebellopontine Angle Tumor, Vestibular Schwannoma	Nystagmus That Coarsens In Amplitude on Lateral Gaze
Brushfield Spots	Downs' Syndrome or Non-Pathological	Greyish-White Spots At Periphery of Iris
Burton Line	Lead Poisoning	Blue Discoloration of The Gingival Border
Cabot Rings	Lead Poisoning, Anemias	Threadlike Strands In Erythrocytes
Caput Medusae	Portal Hypertension	Distended Veins Radiating From Umbilicus
Cardarelli's Sign	Aortic Arch Dilation Or Aneurysm, Mediastinal Tumor	Left Displacement of Trachea Elicits Palpable Pulsation of Same
Carey Coombs Murmur	Rheumatic Fever	Mid-Diastolic Rumble
Carnett's Sign	Abdominal Mass and/or Pain	Supine Patient Lifts Head From Bed; ↑ Pain - Abdominal Wall; ↓ Pain - Intraperitoneal
Carvallo's Sign	Tricuspid Regurgitation	Increase In Volume of Murmur on Inspiration
Casal Collar	Pellagra (Niacin Deficiency)	Widely Variable Collar of Dermatitis Characteristically In C3,C4 Dermatomes
Casoni Test	Hydatid Disease	Intradermal Injection of Hydatid Fluid Causing Wheal
Celsus Signs of Inflammation	Inflammation	1. Rubor (Redness) 2. Tumor (Swelling) 3. Calor (Heat) 4. Dolor (Pain)
Chaddock Reflex	Pyramidal Lesions, Corticospinal Tract Lesions	Extension of Big Toe With Stimulation of Skin Over Lateral Malleolus
Chadwick Sign	Pregnancy	Cyanosis of Vulva, Vagina And Cervix
Charcot's Triad	Ascending Cholangitis	Jaundice, Fever And Chills, RUQ Pain
Charcot's Triad	Multiple Sclerosis	Nystagmus, Intention Tremor, Staccato Speech
Charcot-Leyden Crystals	Any Disorder Characterized By Eosinophil Proliferation, E.G. Ascariasis	Lysophospholipase Crystals In Various Tissues
Cheyne-Stokes Respiration	Respiratory Center Damage	Fluctuation Between Apnoea And Tachypnoea
Churchill-Cope Reflex	Heart Failure	Distension of Pulmonary Vascular Bed Causes Tachypnoea
Chvostek's Sign	Hypokalemia	Tapping Over Facial Nerve Elicits Abnormal Muscle Contraction(S)
Claybrook Sign	Blunt Abdominal Trauma	Heart And/Or Breath Sounds Heard Through Abdominal Wall Indicate Rupture of Viscus
Clutton's Joints	Congenital Syphilis	Painless Symmetrical Hydrarthrosis, Particularly of The Knees
Codman's Triangle	Osteosarcoma, Ewing's Sarcoma	Triangular Subperiosteal Growth
Comby Sign	Rubeola	Whitish Patches on Gingiva And Buccal Mucosa
Comolli's Sign	Scapular Fracture	Triangular Swelling Corresponding To The Outline of The Scapula
Coombs Test	Hemolytic Anemia	
Cornell's Sign	Pyramidal Tract Lesions	Scratching Alongside Big Toe Extensor Tendon Elicits An Extensor Plantar Response

Contd

Contd

Sign	Associated conditions	Description
Corrigan Pulse	Aortic Insufficiency	Carotid Pulsations With Abrupt Ascending And Descending Phases
Councilman Body	Viral hepatitis (Hepatitis C, Yellow Fever, Viral Hemorrhagic Fevers)	Eosinophilic Globules In Liver
Courvoisier's Law	Obstructive Jaundice	Palpable Gall Bladder W/ Painless Jaundice Unlikely To Be Cholelithiasis
Crichton-Browne Sign	'General Paresis'	Tremor At Corners of Mouth And of Outer Canthus
Crowe Sign	Neurofibromatosis Type I	Axillary Freckling
Cruveilhier-Baumgarten Bruit	Portal Hypertension	Bruit Around The Umbilicus
Cullen's Sign	Intraabdominal Hemorrhage (hemoperitoneum)	Ecchymosis Around Umbilicus Predicts Onset of Acute Pancreatitis or ectopic pregnancy
Curschmann Spirals	Asthma	Spiral Mucus Plugs Found In Sputum
Cushing's Triad	Raised Intracranial Pressure	Elevated Systolic Bp, Bradycardia, Irregular Respiration
Dagher Maneuver	Penetrating Pelvic Trauma	Bimanual Palpation of Foreign Object Lodged In Pelvis With One Digit In An Incision Lateral To The Anus And The Other Digit Inserted in The Rectum
Dalén-Fuchs Nodules	Sympathetic Ophthalmia	
Dahl's Sign	Copd	Pigmented Calluses on Anterior Surface of Thighs (From Leaning on Elbows)
Dalrymple Sign	Thyrotoxicosis	Widened Palpebral Opening
Dance's Sign	Ileio-Cecal Intussusception	Empty RLQ (Retracted Right Iliac Fossa)
Darier's Sign	Urticaria Pigmentosa	Dermatographia
Dawson's Fingers	Multiple Sclerosis	Characteristic Fingerlike Appearance of Lateral Ventricle on Mri, Ct, Or At Autopsy
De Musset's Sign	Aortic Insufficiency	Head Nodding In Time With Heartbeat
Dennie-Morgan Fold	Atopic Dermatitis	Accentuated Fold Below The Lower Eyelid
Destot's Sign	Pelvic Fracture	Ecchymosis Superior To Inguinal Ligament, In Scrotum Or of Thigh
Dix-Hallpike Test	Benign Paroxysmal Positional Vertigo	Elicitation of Extreme Vertigo Upon Lateral Movement of A Patient's Head When Lying In A Supine Position
Döhle Bodies	Various Including Trauma And Neoplasm	Basophilic Inclusions In Peripheral Cytoplasm of Neutrophils
Doi's Sign	Eaton-Lambert Syndrome	Reappearance of Absent Deep Tendon Reflexes After Short Period of Maximal Muscle Contraction
Dunphy Sign	Appendicitis	Increase In Abdominal Pain on Coughing
Duroziez's Sign	Aortic Insufficiency	Double Bruit Heard Over Femoral Artery When It Is Compressed Distally (See Traube's Sign)
Elschnig Spots	Hypertensive Retinopathy	
Epstein's Pearls	Normal Newborn	Cystic Papules on Palate
Ewart's Sign	Pericardial Effusion	Percussive Dullness, Aegophony And Bronchial Breath Sounds At L Scapular Tip
Faget Sign	Yellow Fever Typhoid Fever Tularemia Brucellosis Others	The Unusual Constellation of Fever And Bradycardia

Contd

Contd...

Sign	Associated conditions	Description
Finkelstein's Test	Dequervain's Tenosynovitis	
Forchheimer Spots	Rubella	Small Red Spots on The Soft Palate
Fothergill's Sign	Rectus Sheath Hematoma	Anterior Abdominal Mass Which Does Not Cross The Midline And Is Still Palpable When Abdominal Wall Muscles Are Tensed
Fox's Sign	Hemorrhagic Pancreatitis	Ecchymosis of Inguinal Ligament (Blood Tracks Retroperitoneally)
Frank's Sign	Ischemic Heart Disease	Ear Crease Indicating Risk of Heart Disease (Disputed)
Friedreich's Sign	Constrictive Pericarditis, Tricuspid Insufficiency	Collapse of Distended Neck Veins In Diastole
Froment's Sign	Ulnar Nerve Palsy	Patient Required To Hold Paper Between Thumb And Palm (Against Attempt To Withdraw); Ability To Do So Is Assessed
Gailavardin Phenomenon	Aortic Stenosis	Dissociation of Musical And Noisy Elements In Ejection Murmur
Gamna-Favre Bodies	Lymphogranuloma Venereum	Basophilic Cytoplasmic Inclusion Bodies
Gandy-Gamna Nodules	Splenomegaly Due To Portal Hypertension And Sick Cell Disease	Small Yellow-Brown Foci In The Spleen
Garrod's Pads	Repeated Extreme Tension of Extensor Tendon In Interphalangeal Joint	Thickening of Skin And Tissue Over Interphalangeal Joint
Gerhardt's Sign		Controversial: See References
Goetz Sign		Refers to the negative contrast effect seen in the pulmonary artery from non-contrast enhanced blood shunting left to right from the aorta.; Seen during right ventriulography in PDA
Gonda's Sign	Pyramidal Tract Lesions	Flexing Then Suddenly Releasing The 4th Toe Elicits An Extensor Plantar Response
Goodell's Sign	Pregnancy	Softening of The Vaginal Part of The Cervix During The First Trimester
Goodsall's Rule	Anal Fistula	Anatomical Relationships, Differentiation of Fistula Types
Gordon's Sign	Pyramidal Tract Lesions	Squeezing The Calf Muscle Elicits An Extensor Plantar Response
Gottron's Papules	Dermatomyositis	Scaling, Erythematous Eruption Or Dusky Red Patches Over The Knuckles, Elbows And Knees
Gowers' Sign	Muscular Dystrophy	
Graham Steell Murmur	Mitral Stenosis	Pulmonary Regurgitation Murmur In Patients With Pulmonary Hypertension Secondary To Mitral Stenosis
Grey Turner's Sign	Retroperitoneal Hemorrhage	Flank Ecchymosis
Griffith's Sign	Graves' Ophthalmopathy	Lid Lag of The Lower Eyelid on Upward Eye Movement
Gunn's Sign	Hypertension	Av "Nicking" Or "Nipping" In Hypertensive Retinopathy
Hamman's Sign	Oesophageal Perforation W/ Pneumomediastinum	Crepitus In Sync W/ Heartbeat But Not Respiration
Hampton's Hump	Pulmonary Embolus With Infarct	Wedge Shaped Consolidation At Periphery With Base on The Pleura
Hampton's Line	Peptic Ulcer	Line on Barium Meal Indicating Mucosal Oedema Associated With Ulcer
Hannington-Kiff Sign	Obturator Hernia	Absent Thigh Adductor Reflex With Positive Patellar Reflex

Contd...

Contd...

Sign	Associated conditions	Description
Harrison's Groove	Rickets	Rib Deformity At The Lower Thorax
Hatchcock's Sign	Mumps	Tenderness Behind Angle of Jaw (Typically Before Swelling Is Evident)
Heberden's Node	Osteoarthritis	Same As Bouchard's Nodes, But Over Dip Joints
Hegar's Sign	Normal Pregnancy	Softening of Cervical Isthmus Appear in Between 4th And 6th Weeks (Usually)
Hess Test	Capillary Fragility	Appearance of Petechiae After Compression of Arm By Bandage Or Blood Pressure Cuff
Hildreth's Sign	Glomus Tumor	Relief of Pain At Tumor Site Upon Vascular Occlusion of Limb, With Acute Return of Pain on Reperfusion
Hippocratic Face	Impending Death	
Hippocratic Fingers	Chronic Hypoxia	Clubbing of Distal Phalanges
Hirschberg Test	Strabismus	Corneal Reflection Centred (-) Or Not Centred (+) on Pupil
Hoffmann's Sign	Corticospinal Tract Lesions	Tapping Distal Phalanx of 3rd Or 4th Finger Elicits Flexion of Same In Thumb
Hollenhorst Plaque	Hypertension, Coronary Artery Disease, And/Or Diabetes	Cholesterol Embolus(I) of Retinal Artery(les)
Homans' Sign	Deep Venous Thrombosis	Knee Bent, Ankle Abruptly Dorsiflexed, Popliteal Pain
Hoover's Sign (Leg Paresis)	Lower Extremity Paresis	Differentiates Organic From Non-Organic Etiology
Hoover's Sign (Pulmonary)	Copd	Inward Movement of Lower Ribs During Inspiration
Howship-Romberg Sign	Obturator Hernia	Pain From An Obturator Hernia Radiating To Knee
Hutchinson's Freckle	Melanoma	Precancerous Facial Pigmentation
Hutchinson's Pupil	Oculomotor Nerve Lesion	Dilated Pupil on The Side of An Intracranial Lesion Due To third Nerve Compression
Hutchinson's Sign	Herpes Zoster	Lesion on Tip of The Nose Which Can Presage Ocular Herpes Zoster
Hutchinson's Teeth	Congenital Syphilis	Small, Widely Spaced Incisors With Notched Biting Surfaces
Hutchinson's Triad	Congenital Syphilis	Interstitial Keratitis,Nerve Deafness, Hutchinson's Teeth
Janeway Lesion	Infective Endocarditis	Palmar Or Plantar Erythematous Or Hemorrhagic Papules
Jendrassik Maneuver	Hyporeflexia	Compares Patellar Reflex W/ And W/O Distraction
Joffroy's Sign	Exophthalmos In Graves Disease	Lack of Forehead Wrinkling When Patient Looks Up With Head Bowed
John Thomas Sign	Various, Including Reiter's Syndrome	Penile Shadow Points At Affected Hip (+) Or Unaffected Hip (-)
Jolly's Test	Myasthenia Gravis Or Eaton-Lambert Syndrome	Electromyography Test Using Repeated Stimuli To Show Fatiguability In Myasthenia
Jones Criteria	Rheumatic Fever	Criteria Used To Diagnose Rheumatic Fever
Kanavel's Sign	Tenosynovitis of Flexor Digitorum Tendon	(1) Finger Held In Slight Flexion, (2) Fusiform Swelling, (3) Tenderness Along The Flexor Tendon Sheath, And (4) Pain With Passive Extension of The Digit.
Kayser-Fleischer Ring	Wilson's Disease (Hepatolenticular Degeneration)	Ring of Brownish Copper Deposit At Corneo-Scleral Junction

Contd...

Contd...

Sign	Associated conditions	Description
Kehr's Sign	Ruptured Spleen	Referred Pain To L Shoulder
Kelly's Sign		Visible Response of Ureter When Touched (Means of Identifying Same)
Kenawy's sign	Portal hypertension	Venous hum over epigastric region
Kerley Lines	Pulmonary Edema	
Kernig's Sign	Meningism, Meningitis, Subarachnoid Hemorrhage	Hip And Knee Fully Flexed, Extension of Knee Elicits Pain And/Or Opisthotonus
Koebner's Phenomenon	Various Conditions	
Koepe's Nodules	Uveitis	Granulomatous Nodules At Pupillary Margin
Koplik's Spots	Measles	
Korotkoff Sounds	Auscultatory Sphygmomanometry	Korotkoff Described 5 Sounds. Only The First (The Onset of Audible Sound, and Corresponding To Systolic Pressure) And The Fifth (Sound Becomes Inaudible, Corresponding To Diastolic Pressure) Are of Practical Clinical Significance (However, See: Auscultatory Gap)
Kussmaul Breathing	Metabolic Acidosis	Labored Deep Breathing With Normal Or Reduced Frequency
Kussmaul's Sign	Various, Including Right Side Failure	Increased Jugular Distension on Inspiration
Kveim Test	Sarcoidosis	Intradermal Injection of Lymphatic Extract From Known Sufferer; Obsolete
Lachman Maneuver	Anterior Cruciate Ligament Injury	Modified Anterior Drawer Test With Knee In Less Flexion
Ladin's Sign	Normal Pregnancy	Softening of Uterus; Similar To Hegar's Sign
Lancisi's Sign	Tricuspid Regurgitation	Giant V-Wave In Seen In Jugular Vein
Larrey's Sign	Sacroiliitis	Pain In Sacroiliac Area on Sitting Down on Hard Chair
Lasègue's Sign	Lumbar Disc Lesions, Sciatica	Better Known As Straight Leg Raise Test
Leopold's Maneuver		Determination of Fetal Lie
Leser-Trélat Sign	Malignant Neoplasm	Sudden Onset of Multiple Pruritic Seborrheic Keratosis
Levine's Sign	Myocardial Infarction	Patient Clenches Fist Over Chest When Asked To Describe Pain
Lhermitte's Sign	Lesions of Cervical Cord Dorsal Columns Or Caudal Medulla, Ms, Chemotherapy, Behçet's Disease	Electrical Sensation Down The Back And Into Limbs With Neck Flexion Or Extension
Liebermeister's Rule		For Each Fever Degree Celsius An Increase of 8 Beats Per Minute In Cardiac Frequency
Lisch Nodule	Type I Neurofibromatosis	Yellow Brown Hamartom on Iris
Lisker's Sign	Deep Venous Thrombosis	Tenderness on Percussion of Antero-Medial Tibia
Litten's Sign	Infective Endocarditis	Cotton-Wool Exudate In The Retina
Lombard Effect	Malingering Due To Simulated Deafness	Automatic Rise In The Loudness of A Person's Voice When They Speak In Noise
Louvel's Sign	Deep Venous Thrombosis	Increased Pain Along Vein With Valsalva; Proximal Pressure Prevents This
Lowenberg's Sign	Deep Vein Thrombosis	Immediate Pain on Inflating Blood Pressure Cuff Around Calf
Macdonald Triad	Sociopathic Personality Disorder	Enuresis, Firesetting And Animal Torture Predictive of Future Criminal Behavior

Contd...

Contd...

Sign	Associated conditions	Description
Macewen's Sign	Hydrocephalus, Brain Abscess	Resonance on Percussion of Fronto-Temporo-Parietal Suture
Magnan's Sign	Cocaine Dependence	Feeling of Moving Foreign Body Under The Skin
Mantoux Test	Tuberculosis	Intradermal Protein Derivative - Diameter of Wheal Evaluated
Marcus Gunn Pupil	Severe Retinal Disease, Lesion of Optic Nerve Anterior To Chiasm	Relative Pupil Dilatation When Light Swings To The Affected Side
Markle Sign	Appendicitis	Rfq Pain on Dropping From Standing on Toes To Heels
Mayne's Sign	Aortic Insufficiency	Systolic Blood Pressure Drop of >15mmHg on Raising Arm
McBurney's Point	Appendicitis	2/3 of The Way Lateral on A Line From Umbilicus To Anterior Superior Iliac Spine (Corresponds To Junction of Vermiform Appendix And Cecum)
McConnell's Sign	Pulmonary Embolism	Echocardiography Finding of Akinesia of The Mid-Free Wall of The Right Ventricle But Normal Motion of The Apex
McDonald's Sign		Ease in flexing the body of the uterus against the cervix.
McMurray Test	Meniscal Tear	Knee Extended, Valgus Stress Applied, Leg Rotated Produces Palpable Or Audible Click
Means-Lerman Scratch	Hyperthyroidism	Systolic Heart Murmur Similar To Pericardial Rub
Mees' Lines	Arsenic Or Heavy Metal Poisoning	Transverse White Lines Across The Nails
Mellignhoff's Sign	Cutaneous Decompression Sickness	Coughing Or Valsalva Accentuates The Venous Markings of An Erysipeloid Rash
Mentzer Index	Microcytic Anemia	Differentiates Iron Deficiency Anemia From Beta Thalassemia
Miller Fisher Test	Normal Pressure Hydrocephalus	Improvement In Cognitive Function After Withdrawal of Csf During Lumbar Puncture Used To Confirm Diagnosis
Moniz Sign	Pyramidal Tract Lesions	Forceful Plantar Flexion of The Ankle Elicits An Extensor Plantar Response
Möbius Sign	Thyrotoxicosis	Inability To Maintain Convergence of Eyes
Muehrcke's Lines	Hypoalbuminemia, Chemotherapy	Paired Transverse White Lines on Nail Bed
Mulder's Sign	Morton's Neuroma	Transverse Compression of The Forefoot Elicits Pain In The Distribution of The Affected Nerve
Müller's Maneuver	Collapsed Section of Airway	Patient Attempts To Breathe In With Nose And Mouth Closed (Opposite of Valsalva Maneuver)
Müller's Sign	Aortic Insufficiency	Visible Pulsation Or Bobbing of Uvula
Murphy's Punch Sign	Perinephric Abscess	Punch Tenderness At The Costovertebral Angle
Murphy's Sign	Cholecystitis	Hesitation on Inspiration While Gall Bladder Is Palpated
Myerson's Sign	Parkinson's Disease	Inability To Resist Blinking When Glabella Is Percussed
Naegle's Rule	Gestation	Method of Estimating Due Date
Nardi Test	Dysfunction of Sphincter of Oddi	Administration of Morphine And Neostigmine Reproduces Sharp Luq Pain; Not In General Use
Nikolsky's Sign	Various, Including Pemphigus Vulgaris	Mild Shear Stress Applied To Skin Causes Bullae To Form

Contd...

Contd...

Sign	Associated conditions	Description
O'Brien's Test		Test for the shoulder that attempts to test specifically for glenohumeral joint labral tears (and more specifically for SLAP Lesions; superior labral tear from anterior to posterior). A false positive may occur if there is an injury to the rotator cuff or acromioclavicular joint.
O'donoghue's Triad	Knee Injury	Coincidence of Anterior Cruciate Injury, Medial Collateral Injury And Meniscal Tear
Oliver's Sign	Aortic Arch Aneurysm	Caudal Movement of Trachea With Systole
Oppenheim's Sign	Pyramidal Tract Lesions	Irritation Downward of The Medial Tibia Causes Dorsiflexion of Big Toe
Ortolani Test	Congenital Hip Dislocation	Palpable Clunk on Moving Hip
Osborn Wave	Hypothermia	Positive Deflection At Qrs-St Junction
Osler's Node	Various, Including Sbe And Sle	Painful Red Lesions on The Pads of The Fingers And Plantar Surfaces
Osler's Sign	Atherosclerosis	Falsely Elevated Bp Reading Due To Incompressibility of Calcified Vessels
Palla's Sign	Pulmonary Embolism	Enlarged Right Descending Pulmonary Artery on Chest X-Ray
Pastia's Sign	Scarlet Fever	Lines of Confluent Petechiae In Skin Creases (Associated With Scarlatiniform Rash And Strep Pyogenes)
Patrick's Test	Sacroiliitis	External Rotation of The Hip Causes Pain
Peabody's Sign	Deep Vein Thrombosis	Calf Muscle Spasm When Raising The Affected Leg With The Foot Extended
Pemberton's Sign	Retrosternal Mass With Superior Vena Cava Syndrome	Arms Elevated Over Head Elicits Facial Plethora, Distended Neck Veins And Inspiratory Stridor
Phalen's Maneuver	Carpal Tunnel Syndrome	30–60 Seconds of Full Forced Flexion of Wrist Elicits Symptoms
Piskacek's Sign	Normal Pregnancy	Palpable Lateral Bulge At Tubal-Uterine Junction; Present At 7–8 Weeks
Plummer's Nail	Thyrotoxicosis	Onycholysis Especially of Ring And Little Fingers
Pratt's Sign	Deep Venous Thrombosis	Pain Elicited By Compression of Posterior Calf
Queckenstedt's Maneuver	Spinal Stenosis	Bilateral Jugular Vein Pressure During Lumbar Puncture Causes Sudden Rise In Csf Pressure
Quincke's Sign	Aortic Insufficiency	Visible Pulsation In Ungual Capillary Bed
Reynolds' Pentad	Ascending Cholangitis	Charcot's Triad + Hypotension And Altered Mental State
Riesman's Sign	Thyrotoxicosis	Bruit Over Globe of The Eye
Rigler's Sign	Pneumoperitoneum	Gas Outlines Both Mucosal And Serosal Surfaces of Bowel
Rinne Test	Hearing Impairment	Comparison of Air Conduction To Bone Conduction Differentiates Sensorineural From Conductive Deafness
Romaña's Sign	Chagas' Disease	Painless Unilateral Periorbital Swelling
Romberg Test	Dorsal Column Lesions, Cerebellar Lesions, Alcohol Intoxication	Inability To Maintain Posture With Eyes Closed
Rose's Sign	Deep Vein Thrombosis	Warm, Stiff Feeling of Skin When Affected Leg Is Pinched
Rosenbach's Test	Bilirubinuria	Color Produced on Addition of Nitric Acid
Rossolimo's Sign	Pyramidal Tract Lesions	Percussion of The Tips of The Toes Causes Exaggerated Flexion of The Toes
Roth's Spots	Various, Including Sbe And Systemic Vasculitides	Retinal Hemorrhages With Pale Centres Seen At Fundoscopy

Contd...

Contd...

Sign	Associated conditions	Description
Rovsing's Sign	Appendicitis	Palpation of Llq Elicits Pain In Rlq
Rumpel-Leede Sign	Capillary Fragility	Petechiae Seen After Compression By Tourniquet
Russell's Sign	Bulimia Nervosa	Scarring of The Dorsum of One Hand (Contact With Incisors When Purging)
Salus's Sign	Hypertension	Deflection of Retinal Veins At Right Angle Junctions Due To Elongation Or Shortening of Connected Arterioles
Schaeffer's Sign	Pyramidal Tract Lesions	Squeezing The Achilles Tendon Elicits An Extensor Plantar Response
Schamroth's Window Test	Chronic Hypoxia	Identifies Clubbing of Distal Phalanges
Schiller's Test	Cervical Cancer	Affected Areas of Cervix Fail To Stain Brown With Iodine Solution
Schilling Test	Pernicious Anemia, Coeliac Disease, Other Malabsorption Disorders	B12 Radioassay; Rare
Schirmer's Test	Keratoconjunctivitis Sicca, As In Sjögren's Syndrome	Quantifies Lacrimal Secretion
Schober Test	Various Disorders of Lumbar Vertebrae	Quantifies Lumbar Flexion
Sherren's Triangle	Appendicitis	Area of Hyperaesthesia Over The Right Lower Abdomen
Shone's Complex	Congenital Heart Defect	Supravalvular Mitral Ring, Parachute Deformity of Mitral Valve, Subaortic Stenosis And Coarctation of The Aorta
Siegrist Streaks	Malignant Hypertension	Hyperpigmented Streaks Parallel To Choroidal Vessels
Simmonds' Test	Achilles Tendon Rupture	Squeezing of Calf Fails To Produce Plantar Flexion
Sims-Huhner Test	Infertility	Determination of Sperm Count And Motility In A Sample Taken From The Cervical Canal Within An Hour of Intercourse
Sister Mary Joseph Nodule	Various Abdominal Malignancies	Palpable Lymph Node In The Umbilicus
Spurling's Test	Cervical Radiculopathy	Axial Compression And Rotation of Cervical Spine To The Side of Symptoms Causes Pain
Stellwag's Sign	Thyrotoxicosis	Infrequent And/Or Incomplete Blinking, Accompanied By Dalrymple's Sign
Still's Murmur	Subaortic Stenosis, Small Ventricular Septal Defect	Systolic Ejection Sound; Vibratory/Musical; Best Heard At Left Lower Sternal Border
Stransky's Sign	Pyramidal Tract Lesions	Sudden Abduction And Release of Little Toe Causes Extensor Plantar Response
Stroop Test	Various, Including Adhd And Schizophrenia	Reaction Times For Incongruent Stimuli (E.G., Word Red Printed In Blue)
Strümpell's Sign	Spastic Paresis of The Lower Extremity	Failure of Abrupt Passive Flexion of The Hip And/Or Knee To Elicit Dorsiflexion And Adduction of Foot
Terry's Nails	Various Including Hepatic Failure	White 'Ground Glass' Nails; Absence of Lunula
Terry-Thomas Sign	Scapholunate Dissociation	Gap Between The Scaphoid And Lunate Bones on Ap Wrist Radiograph
Thomas Test	Fixed Flexion Deformity of Hip	Supine Patient Flexes One Hip Whilst Keeping Other Leg Flat; Back Arches If Flexion Deformity Is Present
Throckmorton's Reflex	Pyramidal Tract Lesions	Pressure Over Dorsal Big Toe Mtp Joint Elicits An Extensor Plantar Response

Contd...

Contd.

Sign	Associated conditions	Description
Tinel's Sign	Neuritis, Compression Disorders	'Dtp' - Distal Tingling on Percussion
Todd's Paresis	Seizure Disorders	Focal Weakness For As Much As 48 Hours After Seizure
Traube's Sign	Splenomegaly	Dull Percussion Sound Over Traube's Space
Trendelenburg's Sign	Inferior Gluteal Palsy, Other Causes of Hip Abductors Weakness	Pelvic Tilt Contralateral To 'Stance Leg'
Troisier's Sign	Various Abdominal Malignancies, Especially Stomach Cancer	Enlargement of The Left Supraclavicular Lymph Node (=Virchow's Node)
Trousseau's Sign of Malignancy	Various Malignancies, Including Pancreatic	Spontaneous Thrombosis of Multiple Veins, Including Portal Circulation
Trousseau's Sign of Latent Tetany	Hypocalcaemia	In Hypocalcaemia, Occlusion of Brachial Artery Induces Carpal Spasm
Uhthoff's Phenomenon	Multiple Sclerosis	↑ In Neurological Symptoms With Exercise Or Other Increase In Body Temperature
Unterberger Test	Vestibular Lesions	Patient Walks In Place With Eyes Closed; Direction of Rotation Indicates Vestibular Lesion on That Side
Virchow's Node	Various Abdominal Malignancies, Especially Stomach Cancer	Enlargement of The Left Supraclavicular Lymph Node (=Troisier's Sign)
Virchow's Triad	Etiology of Thrombosis	Hypercoagulability, Hemodynamic Changes (Stasis, Turbulence) And Endothelial Injury/Dysfunction
Von Braun-Fernwald's Sign	Pregnancy	Softening of The Uterine Fundus At The Site of Implantation At 4-5 Weeks Gestation
Von Graefe Sign	Graves' Disease	'Lid Lag'; Immobility of Upper Lid on Downward Gaze
Wada Test	Epilepsy, Anatomical Lesions of Cerebrum	Short Acting Barbiturate Injected in Internal Carotid; Lateralizes Language Function
Waddell's Signs	Chronic Pain	Identify Non-Organic Sources of Low Back Pain
Waddell's Triad	Child Pedestrian Stuck By Motor Vehicle	Head Trauma, Thoracic And/Or Abdominal Trauma, Femoral Fracture
Watson's Water Hammer Pulse	Aortic Regurgitation	Bounding Forceful Pulse Elicited With Postural Manoeuvres
Wellen's Sign Or Warning	Severe Stenosis of LAD	Characteristic ECG Changes
Westermarck Sign	Pulmonary Embolism	Area of Oligemia on Chest X-Ray
Wickham's Striae	Lichen Planus	White Or Greyish Lines on The Lichen Planus Lesions
Winterbottom's Sign	Trypanosomiasis	Posterior Cervical Chain Adenopathy
Yeoman's Test	Sacroiliitis	
Hoover's sign	To differentiate organic paresis from malingering or functional weakness	Relies on the principle of synergistic contraction . (Involuntary extension of the "normal" leg occurs when flexing the contralateral leg against resistance.) To perform the test, the examiner should hold one hand under the heel of the "normal" limb and ask the patient to flex the contralateral hip against resistance (while the patient is supine), asking the patient to keep the weak leg straight while raising it.

Contd...

Contd...

Sign	Associated conditions	Description
		If the patient is making an honest effort, the examiner should feel the "normal" limb's heel extending (pushing down) against his or her hand as the patient tries to flex (raise) the "weak" leg's hip. Feeling this would indicate an organic cause of the paresis. If the examiner does not feel the "normal" leg's heel pushing down as the patient flexes the hip of the "weak" limb, then this suggests functional weakness (sometimes called "conversion disorder") or Malingering, i.e. that effort is not being transmitted to either leg.
Wada's test	Used in Epilepsy surgery	Sodium amytal is injected into each internal carotid artery in turn, which stimulates speech and memory testing to localise function. The aim is to confirm language laterality so that resection on the side of the lesion will NOT significantly impair verbal memory functions - used in functional neurosurgery (temporal lobe epilepsy surgery).

TRIADS

Name	Triad	Disease
Alkaptonuria Triad	Ochronotic arthritis, Ochronotic pigmentation, Urine darkens on standing	Alkaptonuria
Anderson Triad	Bronchiectasis, Cystic fibrosis, Vitamin A deficiency	
Beck's Triad	Muffled (<u>D</u> istant) heart sound, <u>D</u> istended neck veins, <u>D</u> ecreased BP (Hypotension)	Cardiac tamponade
Bezold's triad	Diminished perception of deeper tones; Retarded bone conduction; Negative Rinne's test	Otosclerosis
Charcot's cholangitis triad	Pain, Fever, Jaundice	Ascending cholangitis
Charcot's neurologic triad	Scanning speech, Intention tremor, Nystagmus	Multiple sclerosis
Congestive Heart Failure Triad	Tachycardia, Tachypnea, Tender hepatomegaly	Congestive Heart Failure
Cushing's Triad of Increased Intracranial Pressure	Bradycardia, Bradypnea, Hypertension	Head Injuries

Contd.

Name	Triad	Disease
Dieulafoy's triad	Hyperesthesia of the skin, Exquisite tenderness and Guarding over McBurney's point	Acute appendicitis
Fanconi Syndrome Triad	Aminoaciduria, Proteinuria, Phosphaturia	Fanconi Syndrome
Female athlete triad	Eating disorders, Amenorrhea, Decreased bone mineral density	
Gradenigo's Triad	Sixth cranial N. Palsy, Persistent ear discharge, Deep seated retro-orbital pain	Gradenigo's Syndrome
Hemobilia - Triad (Triad of Sandblom)	Malena, Obstructive jaundice, Biliary colic	
Hemolytic Uremic Syndrome Triad	Anemia, Thrombocytopenia, Renal failure	
Hutchinson's Triad	Hutchinson's teeth, Interstitial keratitis, Nerve deafness	Congenital syphilis
Kartagener's Syndrome Triad	Bronchiectasis, Recurrent sinusitis, Situs inversus,	Kartagener's Syndrome
Meckler's triad	Vomiting, Pain and Subcutaneous emphysema	Boerhaave syndrome

Contd...

Contd

Contd...

Name	Triad	Disease
O' Donoghue Triad	Injury to Medial collateral ligament Anterior cruciate ligament Medial meniscus	Twisting force in a weight bearing knee joint
Saint's Triad	Gall stones Diverticulosis Hiatus hernia	
Samter's Triad (aspirin triad)	Aspirin sensitivity Nasal polyps Asthma	Aspirin-induced asthma
Tetany in Children - Triad	Stridor Carpopedal spasm Convulsions	Tetany
Triad of Albinism	Black locks Occulocutaneous Albinism Deafness of sensorineural type	Albinism
Triad of Alport's Syndrome	Sensorineural deafness, Progressive renal failure, Ocular anomalies	Alports Syndrome
Triad of Behcet's Syndrome	Recurrent oral ulcers Genital ulcers Iridocyclitis	Behcet's Syndrome
Triad of Causes of Biotin Deficiency	Glossitis Alopecia Dermatitis	
Triad of Hypernephroma	Pain Hematuria Renal mass	Hypernephroma
Triad of Kwashiorkor	Growth retardation Mental changes Edema	Kwashiorkor
Trotter's Triad	Conductive deafness Immobility of ipsilateral soft palate Trigeminal neuralgia	
Whipple's Triad	Symptoms of hypoglycemia Low blood glucose measured at time of symptoms Symptoms resolved on correction of hypoglycemia	Insulinoma

Contd...

Contd...

Name	Triad	Disease
Vogts triad (also see in ophthalmology under glaucoma)	EPILOIA; Convulsions (EPI lepsy); Mental retardation (LOW IQ) Adenoma sebaceum	Tuberous sclerosis
Borchardt's triad	Upper abdominal pain and distention; Inability to vomit Impediment to nasogastric tube insertion	Acute gastric volvulus
Reynold's Pentad	Abdominal pain Fever Jaundice Shock and Depression of CNS function	Acute suppurative cholangitis

ALTERNATE NAMES

1. **Abetalipoproteinemia:** Acanthocytosis or Bassen-Kornweig syndrome
2. **Adolescent coxa vara:** Slipped capital femoral epiphysis
3. **Adolescent kyphosis:** Scheuermann's disease
4. Ataxia telangiectasia: **Louis-Barr syndrome**
5. Basal cell carcinoma: **Rodent ulcer**
6. Bedsores: **Decubitus ulcers**
7. Boil: **Furuncle**
8. **Burger's disease:** Thromboangiitis obliterans
9. Corn: **Grain**
10. Hurler's syndrome: **Gargoylism**
11. **Kawasaki disease:** *Mucocutaneous lymph node syndrome*
12. **Keratoacanthoma:** Molluscum Sebaceum
13. **Malherbe's epithelioma:** Benign calcifying epithelioma
14. Melorheostosis: **Candle bones (Leri's disease)**
15. Multiple Chondromatosis: **Ollier's disease**
16. **Multiple exostosis:** Diaphyseal Aclasis
17. Nail-Patella syndrome: **Osteo-Onychodysplasia**
18. **Ogilvie's syndrome:** Acute colonic *pseudo-obstruction*
19. **Ormond's disease:** *Idiopathic retroperitoneal fibrosis*
20. **Paget's disease:** *Osteitis deformans*
21. **Port wine stain:** *Nevus Flammeus*
22. **Riley-Day syndrome:** *Familial Dysautonomia*
23. Salmon patch: **Stork bites**

24. Sebaceous cyst: **Wen**
25. **Shock lung:** Adult respiratory distress syndrome
26. **Stye:** Hordeolum *externum*
27. **Takayasu disease:** Pulse less disease
28. Terminal pulp space infection: **Felon**
29. Tibia vara: **Blount's disease**
30. Torticollis: **Wry neck**
31. **Turban tumor:** *Cylindroma*
32. Urticaria: **Hives**
33. **Wilson's disease:** *Hepato lenticular* degeneration.

Autoinflammatory Diseases in Which Fever is Characteristic

- Adult and juvenile Still's disease
- Cryopyrin-associated periodic syndromes (CAPS)
- Familial Mediterranean fever
- Hyper-IgD syndrome
- Behcet's syndrome
- Macrophage activation syndrome
- Normocomplementemic urticarial vasculitis
- Antisynthetase myositis
- PAPA syndrome (Pyogenic Arthritis; Pyoderma gangrenosum and Acne)
- Blau syndrome
- Gouty arthritis

More One-Liners

- **Johannes de Ketham's Fasciculus Medicinæ**, the first illustrated medical text ever printed, show methods of information access and exchange in medical practice during the early Renaissance. Initially published in 1491
- **Well's** clinical prediction rule—for *pulmonary embolism*.
- *Grapefruit (but not orange) juice* inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.
- **Ca-breast** risk assessment models - *GAIL model* and *Claus model*
- MC cause of *primary headache: tension type* headache
- MC cause of *secondary headache: Systemic infection*
- An *orphan drug* is a drug required for *prevention of a rare disease*.
- **Photoretinitis:** A.k.a '*solar retinopathy*' or '*eclipse burn*' - caused due to "*infrared rays*" due to eclipse viewing usually - causes thermal damage and burn to the macula.

- Resolving power of
 - *Direct* ophthalmoscope: **70** microns
 - *Indirect* ophthalmoscope: **200** microns
- The *bruit in thyroid* is palpable/auscultable easily at *upper pole* of thyroid - since superior thyroid artery enters here superficially.
- **Berry's sign:** When carotid pulse is impalpable due to infiltration of carotid sheath by a malignant thyroid swelling - it is called Berry's sign.
- **Tectal beaking on MRI** (fusion of midgrain colliculi into a single beak pointing posteriorly and invaginating into the cerebellum) - seen in *Chiari type II* malformation.
- **Young's prostatectomy** is "radical perineal prostatectomy" - named after Hugh Hampton Young who developed the procedure.
- **Fagerstrom's test** is used to assess the degree of *nicotine dependence*. Score of 0-3 (low); 4-6 (moderate); 7-10 (high nicotine dependence).
- **Medulloblastoma** "exclusively" occurs in the - *cerebellum* (NOT medulla).
- Antemortem diagnosis of *rabies:* **Direct immunofluorescence** to demonstrate rabies virus antigen - samples used are *corneal smears, skin biopsy* (from face and neck) and *saliva*.
- In severe *secondary hyperparathyroidism*, an increase of FGF23 production by osteocytes (and possibly osteoblasts) in bone occurs well before an elevation in PTH is detected - means "**EARLIEST to increase is FGF23**" - even before increase in PTH".
- **Aldosterone antagonists (spironolactone** etc) are the **only diuretics which DO NOT require access to the renal tubular lumen** to induce diuresis (it acts from the interstitial side of the renal tubular cell).
- Side effects of theophylline due to **Adenosine A1 receptor antagonism** are: Diuresis; seizures and cardiac arrhythmias.
- **Primary Biliary Cirrhosis** can lead to hepatocellular carcinoma.
- **Brighton criteria** helps in categorising the level of diagnostic certainty of **Gullain Barre Syndrome** on a scale of 1-4 (1 being most certain).
- **Galactose** binds to focal sclerosis permeability factor in **FSGS** and has been shown to be of benefit in treatment of FSGS.
- **Enteroviruses** are the MC cause of *viral meningitis*.
- **Nagayama's spots** are erythematous papules at the uvulopalatoglossal junction seen in *roseola infantum*.
- **Safinamide** is a monoamine oxidase type B (MAO-B) inhibitor indicated as **adjunctive treatment to levodopa/carbidopa** in patients with Parkinson's disease (PD) experiencing "off" episodes.

- **Structural scoliosis** can be differentiated from postural/sciatic scoliosis by **Adam's test**.
- **Irish's node** is an enlarged left axillary lymph node in gastric Cancer.
- **Scirrhus carcinoma** of stomach diagnosed by double contrast barium meal.
- A prominent posterior calcaneal process (bony spur) is called **Haglund's deformity** which may lead to chronic achillo-tendinitis.
- **Stiff-person syndrome (SPS)**, formerly Stiff-man syndrome, is a rare autoimmune disease usually exhibiting severe spasms and thoracolumbar stiffness, with very elevated **glutamic acid decarboxylase antibodies** (GAD Ab). BUT paraneoplastic SPS is associated with amphiphysin antibodies (amphiphysin Ab). Seen with breast and small cell lung cancers.
- **Asbestos associated cancers**: Mesothelioma and Lung. (Others with inconclusive evidence - throat, esophagus, colorectal, kidney and gallbladder)
- **Pickering syndrome**: Flash pulmonary edema associated with Bilateral renal artery stenosis.
- **Lithium** has anti-suicidal effect.
- **Canagliflozin** has received FDA warning for increased risk of **leg and foot amputations**!
- **Carbamazepine** adverse effects are classified as:
 - **Dosage related**: GIT disturbances; Double/blurred vision; Vertigo; hematologic disturbances; Task performance impairment.
 - **Idiosyncratic**: Agranulocytosis; SJS; Aplastic anemia; Hepatic failure; Rash; pancreatitis.
- Immunohistochemical (IHC) marker for **vascular tumors** (angiosarcoma, hemangioma) : **ERG** (MOST specific and sensitive) > CD 31, CD 34, FLH > vWF (Least sensitive).
- **ALK** (Anaplastic Lymphoma Kinase) gene (chromosome 2p23) - A/w **Inflammatory myofibroblastic tumor**. **Crizotinib** is targeted therapy against ALK.
- **CA19-9** (Carbohydrate antigen 19-9) is a **sialylated Lewis (a) antigen** (a specific biomarker for **pancreatic adenocarcinoma**).
- Methotrexate increases extracellular adenosine levels.
- **Positional Asphyxia**: Body is in "**jack-knife**" position body is in such a position that abdominal organs press upon the diaphragm from below upwards.
- Most pathogenic fungi have **1-3 beta D glucan** in their cell wall and this antigen detection is used for diagnosis of invasive fungal infections. EXCEPTIONS are: *Cryptococcus*, *Zygomycetes*; *Mucor*; *Rhizopus*, *Blastomyces*.
- The hormone with a **permissive action** at the onset of puberty is **Leptin**.
- The **primary event at puberty** is the **pulsatile release of GnRH**.
- **Raymond's syndrome**: Sixth cranial nerve paresis + ipsilateral ataxia + contralateral hemiparesis.
- **Chronotropic Incompetence**:
 - Failure to increase the heart rate with exercise is referred to as chronotropic incompetence. This is alternatively defined as
 - failure to reach 85% of predicted maximal heart rate at peak exercise OR
 - failure to achieve a heart rate >100 beats/min with exercise OR
 - a maximal heart rate with exercise less than two standard deviations below that of an age-matched control population.
- The traditional formula to calculate Age predicted maximal heart rate (**APMHR**) is 220 bpm minus age (220 - Age).
- **Indications for choledochotomy**: palpable duct stones; jaundice or a history of jaundice or cholangitis; a dilated CBD; abnormal LFTs (especially raised alkaline phosphatase)
- **MC cause of Addison's disease** (primary adrenal insufficiency) is **Autoimmune adrenalitis**.
- 60-70% cases of Autoimmune adrenalitis is a/w autoimmune polyglandular syndromes (APS).

CHAPTER

22

Surgery

Author's Note

- Basics of surgery, System-wise surgical topics (which are basically surgery topics) and of course, hardcore surgery topics like hernia, appendix, breast, arterial and venous disorders and general surgery have been discussed in this chapter.
- Pediatric gastrointestinal surgical condition have been covered under pediatrics chapter
- All cancers of various systems have been covered under oncology chapter.

IMPORTANT PEOPLE IN SURGERY

Person	Contribution
Galen	He recognised that this localisation of infection (suppuration) in wounds, inflicted in the gladiatorial arena, often heralded recovery, particularly after drainage (<i>pus bonum et laudabile</i>)
Robert Koch	He laid down the first definition of Infective disease (Koch's postulates -see under microbiology chapter)
Ignac Semmelweis	This Austrian obstetrician showed that puerperal sepsis could be reduced from over 10 per cent to under 2 per cent by the simple act of handwashing between cases.

Contd...

Person	Contribution
Louis Pasteur	He recognised through his germ theory that micro-organisms were responsible for infecting humans and causing disease.
Joseph Lister	Reduced colonising organisms in compound fractures by using antiseptics .
Alexander Fleming	Discovery of penicillin in 1928
Florey and Chain	Penicillin was isolated for clinical use in 1941
Constable Alexander	First patient to receive penicillin (in Oxford town)

Contd...

SURGERY BASICS

WOUND HEALING

Phases of Normal Wound Healing

- **Inflammatory** phase (Day 0 - Day 2)
- **Proliferative** phase (Day 3- 3rd week)
- **Remodelling** phase (maturing phase): Beyond 3rd week.

Classification of Wound Closure and Healing

- **Primary Intention**:
 - Wound edges opposed
 - Normal healing
 - Minimal and **BEST scar**
 - Done in cases of clean wound

- **Secondary intention**:
 - Wound left open
 - Heals by **granulation, contraction and epithelialisation**
 - Increased inflammation and proliferation, poor scar
- **Tertiary Intention (delayed primary Intention)**:
 - Wound **initially left open (due to contamination)**
 - Edges later opposed when healing conditions favourable
 - May require skin grafting
 - Done in infected wounds

Tidy vs Untidy Wounds

- **Tidy**: Incised wound, clean wound, tissues are healthy; tissue loss is rare

- **Untidy:** Crushed or avulsed wound; Contaminated wound; Devitalised tissues; Often tissue loss is present.

Types of Surgical Wounds (Surgeries)

- **Clean** (no viscus opened)
- **Clean-contaminated** (viscus opened, minimal spillage)
- **Contaminated** (open viscus with spillage or inflammatory disease)
- **Dirty** (pus or perforation, or incision through an abscess).

EXTRA EDGE

- **Pressure sores** are tissue necrosis and ulceration occurring due to prolonged pressure. **MC sites are Ischium** > greater trochanter > sacrum > heel > malleolus (lateral > medial) > occiput.
- Applying intermittent negative pressure of approximately **minus 125 mmHg** hastens wound debridement and formation of granulation tissue in chronic wounds and ulcers (*vacuum assisted closure*).

PHYSIOLOGIC RESPONSE TO INJURY

- The *natural response to injury in animals* includes
 - Immobility/rest
 - Anorexia
 - Catabolism
- *Metabolic response to injury in humans* according to Cuthbertson ("Ebb and flow" phases) is as in table below:

Ebb phase	Flow phase	Recovery phase
Lasts for 24-48 hours	Lasts for few days	Lasts for few weeks
Shock	Catabolism	Anabolism

Stages of Shock

Stage	Mechanism	Signs
Compensatory stage	<ul style="list-style-type: none">• Arterial pressure and tissue perfusion are reduced• Compensatory mechanisms activated• Epinephrine and norepinephrine are secreted• Renin-angiotensin-aldosterone system activated• Cardiac output and tissue perfusion are maintained	<ul style="list-style-type: none">• Tachycardia and bounding pulse• Tachypnea• Restlessness
Progressive stage	<ul style="list-style-type: none">• Compensatory mechanisms fail• Tissue becomes hypoxic• Cells switch to anaerobic metabolism; metabolic acidosis occurs• Acidotic state depresses myocardial function• Venous pooling and increased capillary permeability result	<ul style="list-style-type: none">• Hypotension• Narrowed pulse pressure• Reduced stroke volume
Irreversible (refractory) stage	<ul style="list-style-type: none">• Reduced perfusion damages cell membranes• Lysosomal enzymes are released; energy stores depleted• Cells use anaerobic metabolism; lactic acid accumulates• Hypotension occurs• Perfusion to coronary arteries and cardiac output is reduced	<ul style="list-style-type: none">• Unconsciousness• Hypotension worsens• Slow, Cheyne Stokes respiration

SHOCK

Types of Shock

Type of Shock	Examples
Hypovolemic shock (MC type)	Hemorrhage (MC cause); dehydration, vomiting; diarrhea
Cardiogenic	Myocardial infarction; heart failure; valvular heart disease; cardiomyopathy
Obstructive	Cardiac tamponade; tension pneumothorax; pulmonary embolism; air embolism
Distributive	Septic shock (bacteria and viruses) Anaphylactic shock (medications, vaccines, venom) Neurogenic shock (spinal cord injury)

EXTRA EDGE

- In all the above types of shock, **cardiac output is low** and **vascular resistance is high** (except in *distributive shock* where *cardiac output is high* and *vascular resistance is low* due to vasodilation)
- **Endocrine shock (hypo- and hyperthyroidism and adrenal insufficiency)** may present as combination of hypovolemic, cardiogenic and distributive shock.
- In **obstructive shock** there is a **reduction in preload** due to mechanical obstruction of cardiac filling.
- In **distributive shock**, **mixed venous saturation is high**.

Monitoring of shock

Minimum parameters	Additional parameters
ECG, Heart rate	CVP
Pulse oximetry, oxygen saturation	Invasive BP
BP	Cardiac output
Urine output, hourly	Base deficit and serum lactate

Treatment of Shock

- Treat underlying cause.
- Supplemental oxygen.
- Intubation and mechanical ventilation.
- Two **large bore IV lines (16 gauge or higher)** for fluid and drug administration. (REMEMBER: *Increasing gauge number corresponds to lower diameter in needles, i.e 18 gauge is thinner than 16 gauge and so on; whereas in catheters increasing Fr (French) size corresponds to increasing diameter*)
- **Extra measures**
 - In hypovolemic shock: *Pneumatic antishock garment; Packed RBCs*
 - In cardiogenic shock: inotropic drugs, vasodilators, thrombolytic therapy.
- New Drug: **Angiotensin II IV infusion (Giapreza)** - FDA approved to increase BP in septic and distributive shock.
- **Best parameter** for monitoring **septic shock is serum lactate**.

EXTRA EDGE

- **RUSH protocol:** Rapid **U**ltrasound for **S**hock and **H**ypotension. Done by **bedside ultrasound** in critically ill shocked patients.
- The components evaluated in the RUSH exam are
 - **Pump** (Heart): Tamponade, LVEF, and RV size
 - **Tank** (Intravascular): IVC, thoracic and abdominal compartments
 - **Pipes** (Large Arteries/Veins): Aorta and femoral/popliteal veins

HEMORRHAGE

Types of hemorrhage

Type of hemorrhage	Comment
Primary hemorrhage	Occurring immediately due to injury or surgery
Reactionary hemorrhage	Delayed hemorrhage (within 24 hours) and is usually due to dislodgement of clot, slipping of ligature, normalisation of BP or vasodilation

Contd...

Type of hemorrhage	Comment
Secondary hemorrhage	Occurs 7-14 days after injury and is due to sloughing of vessel wall (due to infection, pressure necrosis from a drain or malignancy)

Classification of Hemorrhagic Shock

Class	Blood volume lost as a % of total
1	< 15%
2	15 - 30%
3	30 - 40%
4	> 40%

DAMAGE CONTROL

Damage Control Resuscitation (DCR)

- Anticipate and treat acute traumatic **coagulopathy**
- **Permissive hypotension (low volume resuscitation)** to prevent rise in systolic BP that may rupture an unstable clot! until haemorrhage control is achieved
- Limit crystalloid and colloid infusion to **avoid** dilutional coagulopathy
- **Damage control surgery** to control haemorrhage and preserve physiology.

Damage Control Surgery (DCS)

- DCS involves **staged operative interventions** with periods of **aggressive resuscitation** to salvage **trauma** patients sustaining **major injuries**.
- DCS includes an **abbreviated laparotomy, temporary packing, and closure** of the abdomen in an effort to blunt the physiologic response to prolonged shock and massive hemorrhage.
- Stages of DCS are
 - Stage 1 - Patient selection
 - Stage 2 - **Temporary surgery** for control of hemorrhage and control of contamination/sepsis
 - Stage 3 - **Shift to ICU** and continue resuscitation in the ICU
 - Stage 4 - **Definitive surgery** (definitive anastomoses and vascular reconstructions)
 - Stage 5 - Abdominal **closure**

SURGICAL FLUID PHYSIOLOGY

- **Exogenous intake of fluid** is 2-3 l/24 hrs of which half is contained in solid food.

Contd...

- **Endogenous water** is the water released during the oxidation of ingested food, which is <500 ml/24 hrs.
- **Fluid output** is as follows: Lungs – 400 ml/24 hrs; Skin – 600-1000 ml/24 hrs; Faeces – 60-150 ml/24 hrs; Urine–1500 ml/24 hrs.
- A **minimum urinary output** of 400 ml/24 hr is required to excrete end products of protein metabolism.
- For **pitting oedema** to appear minimum fluid accumulation should be **4.5l**.
- For every 100 mg/dl increase in glucose above normal, the serum sodium concentration is reduced by **1.6 mEq/L**. Therefore hyperglycaemia should be excluded as a cause of hyponatremia before treatment.
- **Buffers:** Most important is **bicarbonate system**
- **Phosphate system:** important for buffering **renal tubular fluid** because it is concentrated in renal tubules.
- **Intracellular protein buffers:** accounts for 75% of body buffering capacity.
- Sodium excretion shutdown of trauma (including postoperatively) occurs for a variable period (up to 48 hours). So immediately excess of 0.9% normal saline should not be given.
- Also, immediately postoperatively; excess loss of potassium also occurs. But the body stores of potassium are so great that, *this does not manifest for 48 hours*:

- **Postoperative energy** and protein requirements depend upon body composition, clinical status and mobility.
- An estimation of requirements is **30 kcal/kg/day** and a **protein intake of 1 g/kg/day** for the average adult patient.

Normal plasma values

➤ Na ⁺	135–145 mEq/L
➤ K ⁺	3.5–5.0 mEq/L
➤ Cl ⁻	98–107 mEq/L
➤ HCO ₃ ⁻	22–28 mEq/L
➤ Ca ²⁺	8.5–10.5 mg/dL (2.2 – 2.5 mmol/l)
➤ Phosphorus	2.5–4.5 mg/dL (0.9 – 13 mmol/l)
➤ Mg ²⁺	1.8–3.0 mg/dL (0.7 – 0.9 mmol/l)
➤ Osmolality	280–295 mOsm/kg

INCISIONS

Scalpel Blades

- No.11 blade: For arteriotomy
- No.15 blade: Minor surgical procedures
- No.22 blade: For abdominal incisions.

Names of Incisions

Name of incision	Procedure
Webster's incision	Circumareolar incision
Gaillard Thomas incision	Submammary incision
McEvedy's incision	Lateral paramedian incision
Turner-Warwick's incision	Placed 2 cm above symphysis pubis and within lateral borders of the rectus muscle Good for exposure of retropubic space
Lazy 'S', Sistrunk's, Modified Blair's	Parotidectomy
Chevron (rooftop) incision	Bilateral subcostal incisions joined together; used for Whipple's procedure; gastrectomy
Kocher's subcostal incision	Open cholecystectomy; muscle cutting oblique incision
Pfannenstiel incision	Cesarean section, Abdominal Hysterectomy (muscle splitting)
Kustner's incision	Transverse incision made 5 cm above the symphysis pubis but below the anterior-superior iliac spine (muscle-splitting)
Maylard incision	A variation of Pfannenstiel incision Rectus abdominis muscles are sectioned transversely to permit wider access to the pelvis (muscle-cutting)
Cherney's incision	Pelvic surgery (muscle-cutting)
Mercedes Benz incision	Superior extension of Chevron incision; used for liver transplant

Contd...

Name of incision	Procedure
Hockey stick incision	Renal transplant
Appendicectomy incisions	See separate table under appendicitis further down in this chapter
Cervicofascial Incision	S-shaped incision for parotidectomy
Tennis racquet incision	Microdochectomy
Wiide's incision	Post-aural incision (mastoidectomy)
Rosen's incision	Stapedectomy (endomeatal or transcanal approach)
Lempert's incision	Endo-aural incision

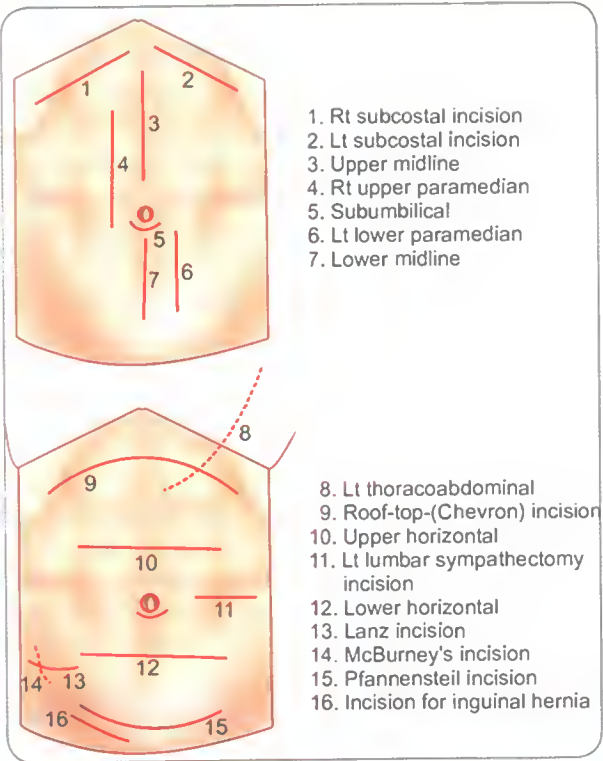
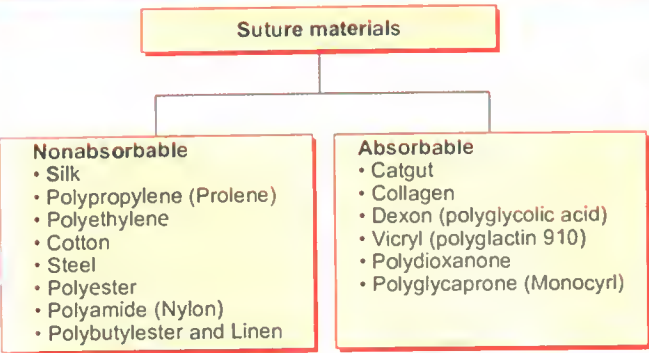


Fig. 22.1: Different incisions in the abdomen.

SUTURES



- **Absorbable sutures:**
 - **Catgut** is made from the **small intestine of sheep or cows**. It is absorbed by phagocytosis in 2 weeks to 6 months. If it is treated with **chromium salts**, the rate of resorption is slower. Catgut is no longer used in developed countries as it causes an inflammatory cellular reaction with release of **proteases** and may also carry the risk of **prion transmission** if of bovine origin.
 - **Polyglycolic acid** absorbed by enzymatic degradation in 2 wks to 2 months
 - **Polydioxanone** is degraded by preliminary hydrolysis and complete absorption and is usually complete by **6 months**.
- **Nonabsorbable sutures:**
 - **Organic sutures** include **silk and cotton**, most reactive.
 - **Synthetic sutures** include **nylon, polypropylene** and **Dacron**
 - **Stainless steel wire and clips** are the **most inert** of the nonabsorbable sutures.

EXTRA EDGE

- The **higher the suture size number**, the **smaller (thinner) the diameter** and the **lower the tensile strength (weaker)**.
- **Monocryl** is used for **subcuticular suturing** after modified radical mastectomy.

Bowel Anastomoses

Type	Features
Lembert suture	Classical seromuscular suture
Senn	Two-layer technique for closure
Halsted	One layer extramucosal closure
Connell	Single layer of interrupted sutures incorporating all layers of the bowel

Contd

Contd...

Contd...

Type	Features
Kocher's	Two-layer anastomosis, first a continuous all-layer suture using catgut, then an inverting continuous (or interrupted) seromuscular layer suture using silk
Matheson	Single-layer extramucosal anastomosis (causes the least tissue necrosis or luminal narrowing).
Cheatele split	(Making a cut into the anti-mesenteric border) may help to enlarge the lumen of distal collapsed bowel
Bowel anastomotic leaks	Generally occur on day 7

EXTRA EDGE

- The "**submucosa**" is the layer of the GIT that provides the **greatest tensile strength** to hold the anastomosed bowel ends together.
- **Jenkin's rule**: For continuous sutures, the length of the suture must be 4 times the length of the wound (4:1).

Ligasure

- '**Ligasure**' tissue fusion technology can **dissect, seal and divide** and was designed to be the only tool that a surgeon would need. However, it is relatively **expensive** to use compared to some of the competing technology.
- It is in wide use in gynaecology, colorectal, urology and general surgery.
- It uses a combination of pressure and energy to create **vessel fusion** which can **withstand up to three times** the normal systolic pressure.

The 'harmonic' Scalpel

- This is an instrument that **uses ultrasound technology to cut tissues while simultaneously sealing them**.
- The scalpel vibrates in the **20,000–50,000 Hz range** and cuts through tissues, effecting haemostasis by sealing vessels and tissues by means of **protein denaturation caused by vibration** rather than heat.
- However, the harmonic scalpel does take **longer to cut and coagulate tissues** than diathermy, and while diathermy can be used to coagulate a bleeding vessel at any time, the **harmonic scalpel can only coagulate as it cuts**.
- Currently, the harmonic scalpel is in common use during laparoscopic procedures, as well as open surgery, such as thyroidectomy and several plastic surgery operations, e.g. cosmetic breast surgery.

INFECTIONS AND SURGERY

- The concept of a '**magic bullet**' (*Zauberbullet*) that could kill microbes but not their host became a reality with the discovery of sulphonamide chemotherapy in the mid-twentieth century.
- The infection of most surgical wounds is referred to as **superficial surgical site infection (SSSI)**. The other categories include **deep SSI** (infection in the deeper musculofascial layers) and **organ space infection** (such as an abdominal abscess after an anastomotic leak).
- The human body harbours approximately **10¹⁴ organisms**.
- Scoring systems for the severity of wound infection (useful in surveillance and research) are the **Southampton and ASEPSIS** systems.
- "**ASEPSIS**" = Additional Treatment; Serous discharge; Erythema; Purulent exudate; Separation of deep tissues; Isolation of bacteria from wound; Stay as inpatient > 14 days as a result of infection.
- Signs of inflammation originally described by **Celsus**: **calor (heat), rubor (redness), dolor (pain), tumor (swelling)** and **functio laesa (loss of function)**, i.e. if it hurts, the infected part is not used).
- **Cellulitis** is the non-suppurative invasive infection of tissues.
- **Lymphangitis** is part of a similar process and presents as painful red streaks in affected lymphatics.
- IV administration of antibiotics **at the induction of anesthesia** is the **optimal time** for giving prophylactic antibiotics before surgery.

Definitions of infected states

- SSI is an infected wound or deep organ space
- Systemic Inflammatory Response Syndrome (**SIRS**) is the body's systemic response to severe infection
- Multiple Organ Dysfunction Syndrome (**MODS**) is the effect that SIRS produces systemically
- Multiple System Organ Failure (**MSOF**) is the end stage of uncontrolled MODS

Synergistic Spreading Gangrene

- A.k.a **subdermal gangrene, necrotising fasciitis**
- A **mixed pattern of organisms** is responsible: *coliforms*, *staphylococci*, *Bacteroides spp.*, *anaerobic streptococci* and *peptostreptococci* have all been implicated, acting in synergy.
- Patients are almost always **immunocompromised** with conditions such as *diabetes mellitus*.

- **Meleney's synergistic hospital gangrene: Abdominal wall infections**
- **Fournier's gangrene: scrotal infection**.

MINIMAL ACCESS SURGERY

Minimal Access Surgery (MAS) Includes

- Laparoscopy
- Thoracoscopy
- Endoluminal endoscopy
- Perivisceral endoscopy
- Arthroscopy and intra-articular joint surgery.

Advantages of Minimal Access Surgery (MAS)

- Decrease in wound size
- Reduction in wound infection, dehiscence, bleeding, herniation and nerve entrapment
- Decrease in wound pain
- Improved mobility
- Decreased wound trauma
- Decreased heat loss
- Improved vision
- Faster recovery and shorter hospital stay

LAPAROSCOPY

- Needle used for pneumoperitoneum: **Veress needle**
- Most commonly used gas: **CO₂**
- Flow of gas: **1L/min**
- Intra-abdominal pressure: **12–15 mm Hg**
- **Trocar** is inserted at or just below the umbilicus penetrating skin, superficial and deep fascia, fascia transversalis and Parietal peritoneum.
- **Post-laparoscopy shoulder pain** is due to **CO₂ retention** causing irritation of diaphragm and referred pain to the shoulder through phrenic nerve.

Gases Used in Pneumoperitoneum

- **First pneumoperitoneum** was created by **filtered room air**
- **CO²** and N₂O are now preferred because of **increased risk of gas embolism with room air**.
- CO₂: 200 times more diffusible than O₂, rapidly cleared from the body and lungs, doesn't support combustion.
- N₂O: 68% as rapidly absorbed in blood as CO₂, have mild analgesic effect, used for short operative procedures like sterilization or drilling.
- For prolonged laproscopic procedures, N₂O should NOT be preferred because it supports combustion better than air.

- **Veress needle** is used for creating **pneumoperitoneum**.
- **SILS** = Single Incision Laparoscopic Surgery; a.k.a laparoendoscopic single site surgery (**LESS**) and single port access (**SPA**) - uses single incision **through umbilicus**.
- Natural orifice transluminal endoscopic surgery (**NOTES**): whereby surgeons enter the peritoneal cavity via endoscopic puncture of a hollow viscus (ex: transgastric and transcolonic); truly scarless surgery.

Physiological Changes in Laparoscopy

Increased	Decreased
<ul style="list-style-type: none">▪ Heart rate▪ Mean arterial pressure (MAP)▪ Central venous pressure (CVP)▪ Pulmonary capillary wedge pressure (PCWP)▪ Systemic vascular resistance▪ Intracranial pressure (ICP)	<ul style="list-style-type: none">▪ Cardiac output.▪ FRC and compliance of lung▪ pH due to <i>increased arterial pCO₂</i>▪ Splanchnic circulation, renal blood flow, GFR and urine flow

Gas Embolism

- MC seen during induction of pneumoperitoneum at the time of insufflations of gas from unintended insufflations of gas directly into an open vein.
- The more soluble a gas in the blood, the lower chances are for gas embolism.
- CO₂ is preferred for pneumoperitoneum as it is highly soluble in blood and is rapidly eliminated.
- CO₂ embolism: An initial rise in ET-CO₂, due to pulmonary excretion of absorbed CO₂ is followed by a sudden decrease due to fall in cardiac output.

Complications of laparoscopy

- Vascular injury
- Diaphragmatic injury
- Bile duct injury
- Gas embolism
- Pneumothorax
- Visceral injury

EXTRA EDGE

- **Capacitance coupling** is a phenomenon in which a capacitor is created by having an insulator sandwiched between two metal electrodes.
- The **most likely** situation for capacitance coupling is a metal cannula with a plastic grip.
- The **least likely** is a plastic grip with a plastic cannula (**completely plastic ports**).

BURNS

Traditional and Current Classifications of Burns

Current nomenclature	Traditional nomenclature and examples	Clinical findings
Superficial thickness (Epidermis involvement)	First degree Sunburn, friction burn, scald	Erythema, minor pain, lack of blisters
Superficial partial thickness [Superficial (papillary) dermis]	Second degree	Blisters, loss of epidermis, Pinprick sensation is normal (pain present), heal without residual scarring in 2 weeks; treatment is non surgical
Deep partial thickness [Deep (reticular) dermis]	Third degree Fat burns	Whiter appearance, reduced sensation, takes 3 or more weeks to heal without surgery and leads to hypertrophic scarring
Full thickness (Epidermis, Dermis, and partial damage to subcutaneous fat, eschar formation and minimal pain, requires grafts)	Alkali and acid burns	No pain is felt, completely anesthetic lesions, hard and leathery feel

EXTRA EDGE

- It should however be noted that although *fourth-degree* is not a technical term, it is often used to describe burns that reach *muscle and bone*. Third-degree sufficiently describes all burns of this nature.
- For more on burns see Forensic Medicine chapter (Pg 519).

Fluid Replacement in Burns Patient

- Muir and Barclay formula**

$$\{\text{weight (kg)} \times \% \text{ burn}\} / 2 = \text{mL colloid per unit time.}$$
 Also give 1.5-2.0 mL/kg/h 5% dextrose.
- Parkland formula (isotonic formula)**

$$4 \times \text{weight (kg)} \times \% \text{ burn} = \text{mL Hartmann's solution in 24h, half given in first 8h (unsatisfactory in children).}$$

SKIN GRAFTS

Split Thickness Skin Grafts (Thiersch Graft)

This contains the **epidermis** and a portion of the dermis. (0.010–0.025 inch). The *abdomen, buttocks and thighs* are common donor sites.

Advantages include:

- Large supply of donor areas and ease of harvesting.
- Availability of donor site for reuse in 10–14 days.
- Decreased primary contracture.
- Skin can be stored for later use.

Disadvantages:

- Cosmetically inferior to full thickness skin grafts

Contd...

Split Thickness Skin Grafts (Thiersch Graft)

- Decreased durability
- Hyperpigmentation
- Increased secondary contracture.

Full Thickness Skin Grafts (Wolfe graft)

This contains the *epidermis and full thickness of the dermis without subcutaneous fat*. They are most useful for *covering defects on the face or hand* that are not amenable to coverage with a skin flap. Preauricular grafts provide the best colour match for the face.

Advantages include:

- Cosmetic superiority to split thickness grafts
- Decreased secondary contractures
- Increased durability.

Disadvantages:

- Limited donor sites
- Increased primary contracture

Survival of Skin Grafts

- During the **first 48 hours**: Imbibition of plasma supports survival. Fibrin is laid down and helps to hold the graft in place.
- By the **fourth to seventh day**: Inosculation (vascular budding) occurs and the graft is supported by a true circulation. **Lymphatic connections** are formed by the **fifth day**.
- Bone denuded of periosteum, cartilage devoid of perichondrium and exposed tendons do not support skin grafts. These areas require a flap procedure.

Contd...

GASTROINTESTINAL SYSTEM

ESOPHAGEAL DISORDERS

Foreign Bodies in the Esophagus

- MC** is a **food bolus**, which usually signifies underlying disease. An impacted food bolus will often break up and pass on if the patient is given **fizzy drinks** and confined to fluids for a short time.
- It is usually possible to remove foreign bodies by **flexible endoscopy**.
- Beware of **button batteries** in the oesophagus (may **corrode the GIT**)—best removed by basket snare - similar to the one used for gallstones.

Esophageal Perforation

- The **MC cause of perforation of esophagus is iatrogenic** (75%).
- MC site of iatrogenic perforation is cervical esophagus**.
- Usually occurs at anatomic sites of narrowing, i.e. cricopharyngeus and GE junction.
- Toilet cleaners** contain **caustics**, which can lead to **stricture** of esophagus as a complication.
- Clinical signs: **Dysphagia, pain**, fever, leukocytosis, tachycardia, respiratory distress and shock.
- Cervical perforations may present with **neck stiffness** and **subcutaneous emphysema** (pathognomonic).
- Intrathoracic perforation: Chest pain, subcut emphysema, dyspnea and **pleural effusion**.
- Definitive management requires **operative repair**.
- ALSO KNOW—in corrosive esophageal stricture, **endoscopy** is the investigation of choice.
- Perforations of **cervical esophagus maybe managed conservatively** while thoracic esophageal perforations almost always require surgery. This cervical perforations have better prognosis compared to thoracic perforations.
- Since plain x-rays are insensitive, **contrast esophagogram** (also called 'water soluble contrast series') using **low-osmolar water soluble ionic contrast medium** is the **first investigation of choice** in suspected perforations. (NOT barium!).

Boerhaave's Syndrome

- Spontaneous full thickness rupture of esophagus** due to **forceful vomiting** (against a closed glottis) with a **full stomach**.
- MC at the **cardiac/lowest constriction**; may occur after alcohol ingestion.

- Clinically **vomiting, lower thoracic pain and subcutaneous emphysema** (**Mackler triad**), **pneumomediastinum** (Crackling sound on chest auscultation - "**Hamman's crunch**"), left pleural effusion.
- Treat with resuscitation, broad spectrum antibiotics and surgical repair.

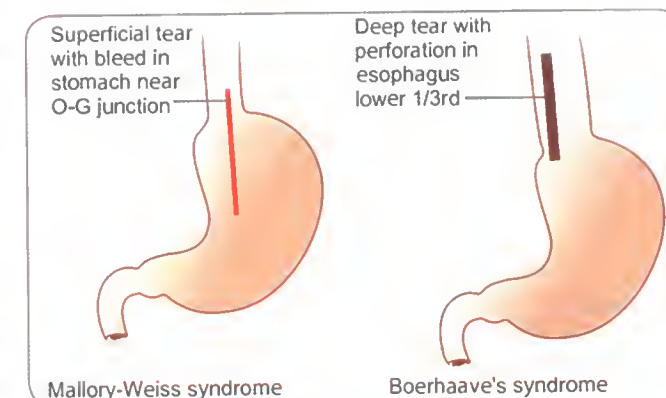


Fig. 22.2: Diagrams showing Mallory-Weiss syndrome and Boerhaave's syndrome

Factors that Favor Operative Repair in Esophageal Perforation

- Large septic load
- Septic shock
- Pleura breached
- Boerhaave's syndrome
- Perforation of abdominal oesophagus.

Mallory-Weiss Tear

- A **vertical tear/split in the gastric mucosa, immediately below the squamocolumnar junction at the cardia** in **90% of cases** (on lesser curvature).
- In only 10%, the tear is in the esophagus.
- Occurs following **retching/vomiting after alcohol** ingestion.
- Presents with **upper GI bleeding/hematemesis**; mainly affects **Left Gastric artery**.
- Diagnosed by **endoscopy**;
- In most patients, **bleeding ceases spontaneously** in **7–14 days**; continued bleeding may respond to vasopressin therapy or **angiographic embolization**.

Gastroesophageal Reflux Disease (GERD)

- Risk factors**: **Obesity, reduced LES pressure**; reduced esophageal clearance mechanism; **delayed gastric emptying**.

- **Triad** of symptoms: Heart burn (*pyrosis*); **Odynophagia** (painful swallowing); **regurgitation** of esophageal content.
- May be a/w **hiatus hernia** (MC sliding type)
- **24-hour pH** recording is the '**gold standard**' for diagnosis of GERD.
- **TLOSRS** (transient lower oesophageal sphincter relaxations) are the **most important manometric findings** in GERD.
- **DeMeester's scoring** system is a global measure of esophageal acid exposure; score > 14.72 indicates reflux - indicates severity of GERD.
- **On endoscopy**, **Savary Miller** and **Los Angeles classifications** are used for classifying GERD.
- **Bernstein test** (HCl instillation) used to reproduce symptoms.
- **Feline esophagus** maybe seen in barium swallow (as per most gastroenterology textbooks).
- **S-shaped (sigmoid) lower oesophagus**,
➤ **Incoordinated peristalsis**.
- Strategies to overcome dysphagia:
 - Arching the neck and shoulders
 - Raising the arms
 - Standing or sitting up straight during the meal
 - **Walking around after a meal.**
- **Esophageal manometry confirms** diagnosis.
- Chronic achalasia - risk for **squamous Ca esophagus**
- Treatment:
 - **Pneumatic balloon Dilatation** and **Negus hydrostatic dilatation** of the LES.
 - Endoscopically guided injection of **botulinum toxin** A directly into the LES reduces LES pressure.
 - **Amyl nitrate** inhalation causes LES relaxation in achalasia but NOT in pseudoachalasia.
 - Surgical: **Heller's cardiomyotomy**.

Treatment of GERD

- **Mainly Medical: Drugs: Proton Pump Inhibitors** are the **DOC** (omeprazole and other prazoles); **H2 antagonists** (antacids); **Prokinetic drugs** (cisapride, omepridone, metoclopramide etc); **Anticholinergic drugs** (pirenzepine); **mucosal protectors** (sucralfate, colloidal bismuth); **defoaming agents** (simethicone, alginic acid).
- **Endoluminal therapies: Suturing** (Wilson Cook); **Plexiglass gelatin microspheres**; **Stretta catheter**.
- Surgery: **Fundoplication** (**Nissen-360°** and others); **Besley mark IV (270°)** operation; **Hill gastropexy**.
- Laparoscopic fundoplication is the most popular technique.
- **Gas-bloat syndrome**: complication of Nissen fundoplication where there is inability to belch and postprandial fullness.

Achalasia

- Achalasia means failure to relax.
- Achalasia is an idiopathic **motility disorder** characterized by loss of peristalsis in the distal two-thirds (smooth muscle) of the esophagus and **impaired relaxation of the lower esophageal sphincter** (LES). There appears to be denervation of the esophagus resulting from **loss of ganglion cells in Auerbach's plexus**.
- **Chagas' disease** (Trypanosoma) causes symptoms similar to severe achalasia.
- Gradual, **progressive dysphagia** for solids and liquids.
- Radiologic findings:
 - Air-fluid level in the enlarged, fluid-filled esophagus, **smooth narrowing** of lower oesophagus (**bird's beak**),
 - **Lack of gas bubble in stomach**,



Fig. 22.3: X-ray picture of achalasia cardia



Fig. 22.4: Heller's cardiomyotomy for achalasia cardia. Only circular muscle layer is cut longitudinally in OG junction until mucosa protrudes out without perforating the mucosa

EXTRA EDGE

- **Pseudoachalasia** is an achalasia-like disorder that is usually produced by **adenocarcinoma of the cardia**, but has also been described in relation to benign tumors at this level.

Diffuse esophageal spasm	Tertiary contractions seen on barium swallow as " corkscrew " or " rosary bead " esophagus
Dysphagia lusoria	due to compression by an aberrant Right subclavian artery
Nutcracker esophagus	Manometrically defined syn. characterized by high amplitude (>180 mmHg) peristaltic contractions; causes chest pain and dysphagia; Treat with CCBs and anticholinergic agents
Schatzki's ring	thin submucosal web completely encircling the whole of the lumen near the middle of the lower sphincter produces dysphagia when the lumen diameter is less than 1.3 cm. Treat by dilatation

Esophageal Diverticula

- **Pulsion diverticula: MC**; these are **false diverticula** containing **mucosa and submucosa** only; it is due to high intraluminal esophageal pressure due to esophageal motility disorders. Examples are:
 - **Pharyngoesophageal (Zenker's) diverticulum**: It is an **acquired pulsion diverticulum** arising from a triangular weakening of (**Killian's triangle**) in the posterior midline of the lower pharynx, between the oblique (**thyropharyngeus**) and transverse (**cricopharyngeus**) muscle fibers of the **inferior pharyngeal constrictor**. Believed to result from cricopharyngeal dysfunction and causes dysphagia. Surgery is curative with a **cricopharyngeal myotomy**, with/without excision of diverticulum and repair of defect.
 - **Epiphrenic diverticulum**: **Acquired pulsion diverticulum** in lower oesophagus a/w achalasia or diffuse spasm. If asymptomatic, no treatment needed.
- **Traction diverticulum**:
 - A **true diverticulum** since it **contains all layers** in its wall and is due to traction by healing fibrosing mediastinal lymph nodes - **secondary** to mediastinal inflammatory diseases (usually granulomatous disease, i.e. TB, Histoplasmosis).
 - Usually a **mid-esophageal or parabronchial** diverticulum.
 - Usually **asymptomatic** and treatment (excision) is not needed. BUT treat the causative disease.

Hiatus Hernia

- **Obesity** is a risk factor.
- Common in **elderly with abdominal/chest pain, postprandial bloating, dysphagia**.
- Treatment: Mainly Surgical.
- **Sliding (MC—85%)**:
 - Axial herniation of the stomach results in the oesophagogastric junction lying above the diaphragm.
 - a/w gastro-oesophageal reflux (GER).
- **Para-esophageal (Rolling)**:
 - A **true hernia** where the stomach (or greater curvature only) herniates through an often enlarged hiatus adjacent to the oesophagus (usually **anterolaterally**) into the mediastinum.
 - Potentially dangerous since a/w volvulus.
 - As the oesophagogastric junction is not displaced this type is **NOT a/w GER**.
 - Ischemic longitudinal ulcer in herniated stomach in rolling ulcer is called **Cameron ulcer**.
 - On **CXR**, the hernia may be visible as a **gas bubble, often with a fluid level behind the heart**.
 - A **barium meal** is the best method of diagnosis.
 - Treatment: Surgical repair
- **Mixed**: combination of above two hernias.

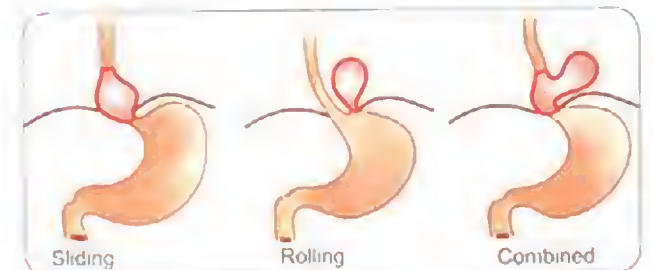


Fig. 22.5: Different types of hiatus hernia

Saint's triad

- Hiatus hernia
- Colonic diverticulosis
- Gallstones.

Barrett's Esophagus

- Distal esophageal **squamous epithelium** is replaced by **metaplastic columnar epithelium** containing **mucus secreting goblet cells** (**intestinal metaplasia**). In response to **prolonged gastro-esophageal reflux**; ↑ risk of **adenocarcinoma** (0.5%/year).

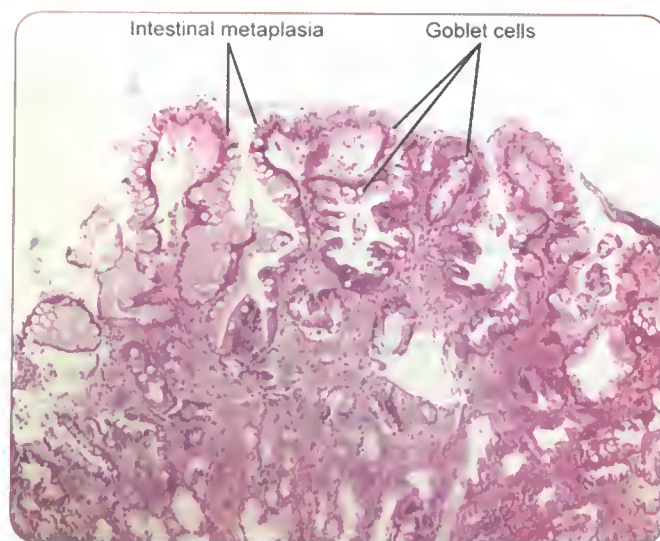


Fig. 22.6: Barrett esophagus with intestinal metaplasia containing goblet cells.

- The risk of cancer increases with increasing length of abnormal mucosa.
- **Classic Barrett's** (3 cm or more columnar epithelium);
- **Short segment Barrett's** (less than 3 cm of columnar epithelium).
- **Cardia metaplasia** (intestinal metaplasia at the esophagogastric junction without any macroscopic change at endoscopy).

Plummer-Vinson Syndrome

- Also called the **Paterson-Kelly syndrome** or **sideropenic dysphagia**.
- Esophageal (**hypopharyngeal, postcricoid**) webs, **glossitis, koilonychia** and **iron deficiency anemia** in **middle-aged women**.
- **Premalignant** condition → **squamous cell Ca** of hypopharynx.

STOMACH DISORDERS

Helicobacter pylori

- **Warren and Marshall** were awarded the **Nobel Prize** for Physiology or Medicine in **2005** for their discovery of the bacterium **Helicobacter pylori** and its role in **gastritis and peptic ulcer disease**. Marshall ingested the bacteria to prove that **H. pylori** was indeed the causative organism!!!
- Two factors that predispose to higher colonization rates include **poor socioeconomic status and less education**.
- **Transmission** of **H. pylori** occurs from person to person, following an **oral-oral or fecal-oral** route.

- In **developing countries**, **80%** of the population may be infected by the age of 20.
- It is a **gram-negative microaerophilic rod**; it is **S-shaped** and contains **multiple sheathed flagella**.
- It produces **urease** — Hydrolyses urea to produce **ammonia**, an essential step in alkalinizing the surrounding pH.
- The effect of ammonia on the antral G cells is to cause the release of **gastrin** — **Causes gastric acid hypersecretion** — Leading to peptic ulcer disease.
- **H. pylori** is now classed by the WHO as a **class I carcinogen**.
- **H. pylori** associated diseases are:
 - Chronic gastritis
 - Peptic ulcer disease
 - Gastric MALT lymphoma
 - Gastric cancer.

Tests for Diagnosis of H. pylori

Invasive (Endoscopic biopsy required)	
Rapid urease	Simple, rapid, false negative with recent use of PPIs, antibiotics or bismuth compounds, cannot be used for early follow-up. Some commercial kits inaccurate before 24h
Histology	Requires pathology processing and staining; provides histologic information; needs pathologist
Culture	Allows determination of antibiotic susceptibility, time consuming, expensive
Noninvasive	
C13 or C14 urea breath test	Simple; rapid; useful for follow-up after treatment; low dose radiation exposure with C14 test
Stool antigen test	Simple, useful for follow-up after treatment, maybe useful in children
Serology	Cannot be used for early follow-up

Indications for H. pylori Eradication

Definite	Not indicated	Uncertain
Peptic ulcer (duodenal and gastric ulcer)	Asymptomatic	Family history of gastric Ca
MALToma	Gastro-esophageal reflux disease	Non ulcer dyspepsia
		Long term NSAID users

Regimens for H. pylori Eradication

Triple Therapy	
➤ Bismuth subsalicylate + Metronidazole + Tetracycline (BMT)	
➤ Omeprazole (Lansoprazole) + Clarithromycin + Amoxicillin (OAC or LAC)	
➤ Ranitidine bismuth citrate + Tetracycline + Clarithromycin or metronidazole (RTC)	

Quadruple Therapy

- Omeprazole (lansoprazole) + Bismuth subsalicylate + Metronidazole + Tetracycline

Gastritis

Acute gastritis	
Risk Factors	Clinical Features
<ul style="list-style-type: none"> • Excess NSAID's, • Alcohol, • Tobacco, • stress (extensive burns — Curling's ulcers, Brain injury — Cushing's ulcers), • ischemia, • Trauma, • H. pylori infection. 	<ul style="list-style-type: none"> • Epigastric pain, • Erosive, acute inflammation, necrosis and hemorrhage, • Hematemesis (coffee ground vomit), • Melena, • Anemia, • Blood in nasogastric tube

Chronic atrophic gastritis	
Risk Factors	Clinical Features
<ul style="list-style-type: none"> • Type A (fundal) — Autoimmune, pernicious Anemia • Type B (antral) — H. pylori. 	<ul style="list-style-type: none"> • Non-erosive, • Mucosal inflammation and atrophy of mucosa, • Risk factor for gastric AdenoCa, and MALT lymphoma

UNCOMMON FORMS OF GASTRITIS

Lymphocytic gastritis	<ul style="list-style-type: none"> • T-lymphocytic infiltration of gastric surface epithelium • Fluctuating abdominal pain, nausea, and vomiting • Endoscopically mucosal erosions and a varioliform appearance ("varioloform gastritis") • May be a/w H. pylori, celiac disease; there is no established effective therapy.
Eosinophilic gastritis	<ul style="list-style-type: none"> • Eosinophilic infiltration of stomach wall with circulating eosinophilia. • Treatment with corticosteroids is beneficial in majority of patients.
Granulomatous gastritis	<ul style="list-style-type: none"> • Seen in Crohn's disease, sarcoidosis, syphilis, fungi, TB, idiopathic

GASTRIC VERSUS DUODENAL ULCERS

Characteristic	Gastric Ulcer	Duodenal Ulcer
Patients, Cause	Age >50 years NSAID users H. pylori infection (minor) Blood type A (gA stria)	Younger H. pylori infection (almost 100%) Blood type O (duO dinal)

Contd...

Characteristic	Gastric Ulcer	Duodenal Ulcer
Frequency	25% cases	75% cases (more common)
Timing of pain	Soon after eating	2–4 hours after eating, night pain (" Duo " = 2 hrs)
Vomiting	Considerable vomiting	No vomiting
Hemorrhage	Hematemesis more frequent than melena	Melena more frequent
Gastric acid level	Normal/low	High
Gastrin level	High	Normal
Effect of eating	Pain increases with meals — afraid to eat - weight loss .	("Pain Decreases with meals in Duodenal ulcer! ") — good appetite - weight gain .
Diet	Lives on milk and fish	Eats almost anything
Sex	Equal in both sexes	MC in males

EXTRA EDGE

- Causes of peptic ulcers = "**HANG MATS**" = **H. pylori**, **Aspirin**, **NSAIDs**, **Gastrinoma (ZES)**, **MEN type I**, **Alcohol**, **Tobacco**, **Steroids**.
- **Flexible endoscopy** is the '**gold standard**' investigation of the upper GIT. For peptic ulcers this is **gastroduodenoscopy**.
- **Endoscopic ultrasound** is the most sensitive technique in the evaluation of the '**T**' stage of **gastric cancer** and in the assessment of duodenal tumors

BENIGN AND MALIGNANT GASTRIC ULCERS COMPARED

Benign gastric ulcer	Malignant gastric ulcer
• Regular smooth margin	• Irregular , raised margin
• 95% in lesser curvature	• MC in greater curvature
• Granulation tissue in floor	• Necrotic slough in floor
• Radiating mucosal folds upto the margin	• Thickened distorted effacing folds do not reach ulcer edge
• Punched or sloping edge	• Everted edge
On Barium swallow:	On Barium swallow:
• Hampton's line: Heaped overhanging mucosa at the margins of benign ulcer projects inwards toward the ulcer	• Kirklin complex: Heaped margins of the malignant gastric ulcer, which touch. This projects as a lucent rim around the ulcer on barium

Contd...

Contd.

Could

Benign gastric ulcer	Malignant gastric ulcer
<ul style="list-style-type: none"> Niche on the lesser curvature with notch on the greater curvature 	<ul style="list-style-type: none"> meal with compression of antr abdominal wall. Carmali's meniscus sign: Semicircular (meniscoid) configuration of malignant gastric ulcer seen in profile with compression of antr abdominal wall

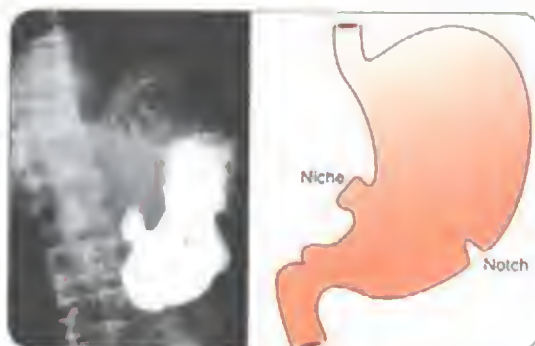


Fig. 22.7: Barium meal study showing niche and notch—gastric ulcer



Fig. 22.8: Absence of duodenal cap—chronic duodenal ulcer

Types of Gastric Ulcers (Daintree Johnson)

Type	Location	Incidence (%)	Acid level
I	In the antrum , near the lesser curve	55 (MC)	Normal
II	Combined gastric ulcer in the body) with duodenal ulcer	25	High
III	Prepyloric ulcer (pyloric channel ulcer)	15	High
IV	Gastric ulcer in the proximal stomach or cardia near GE junction	5	Normal

EXTRA EDGE

- Often in the lesser curve of stomach, **saddle shaped** ulcer can occur.
- Type V** gastric ulcer is **ulcer anywhere** in the stomach a/w NSAIDs.

Complications of Gastric Ulcer

- Perforation:** MC complication
- Hourglass** stomach: Exclusively seen in women due to cicatricial contracture of lesser curve ulcer.
- Tea pot (Hand bag)** stomach: due to cicatrization and shortening of lesser curvature.
- Bleeding** by erosion into **left gastric artery**; MC with type II and III ulcers.
- Malignant transformation** into AdenoCa stomach in 5-10%.

Complications of Duodenal Ulcer

- Pyloric stenosis
- Bleeding, perforation, residual abscess, penetration to pancreas.

EXTRA EDGE

- Chronic duodenal ulcer will NOT turn into malignancy.
- Ulcer > 2 cm is called **giant duodenal ulcer**.
- Meteorism** is acute sudden gastric dilatation seen in septicemia, uremia and hypokalemia.
- Valentino's** syndrome: Perforated peptic ulcer mimicking appendicitis.

SUMMARY OF OPERATIONS FOR GASTRIC ULCER (GU)

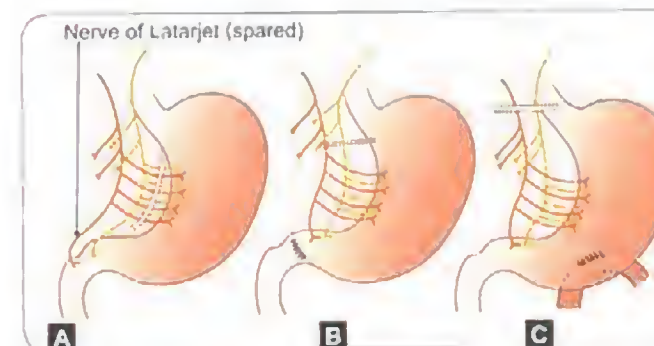
- Billroth I:** Partial gastrectomy with simple re-anastomosis. This has been the classic operation of choice.
- Billroth II, (Polya gastrectomy):** Resection of the stomach below a high benign GU invariably results in healing of the ulcer. The duodenal stump is oversewn (leaving a blind loop), and anastomosis is achieved by a longitudinal incision further down the duodenum.
- Vagotomy and pyloroplasty:** With frozen section biopsy of the GU (if benign) is advocated as a conservative operation for GU.
- Proximal gastric vagotomy:** With excision of the ulcer has also been described.
- Ulcers located near the esophagogastric junction may require a more radical approach, a **subtotal gastrectomy with a Roux-en-Y esophagogastric anastomosis (Csende's procedure)**. A less aggressive approach, including antrectomy, intraoperative ulcer biopsy, and vagotomy (**Kelling-Madlener procedure**), may be indicated in fragile patients with a high GU.

EXTRA EDGE

- Pseudo-Billroth-1** appearance on Barium swallow is seen in Crohn's disease.

SUMMARY OF OPERATIONS FOR DUODENAL ULCER

- Vagotomy with or without gastric drainage:** This is the **classic operation**. Vagotomy reduces acid production from the stomach body and fundus, and reduces gastrin production from the antrum. **However**, it interferes with emptying of the pyloric sphincter and so a drainage procedure must be added. The commonest is a **pyloroplasty** in which the pylorus is cut longitudinally and closed transversely. A **gastrojejunostomy** is an alternative. Three types of vagotomy are:
 - Truncal vagotomy:** Both trunks of the vagus nerves are transected. In fact, about, 5-7 cm of the nerve are excised so that this technique can be referred to as "vagotomy!"
 - Selective vagotomy:** Is aimed at removal of all gastric fibres of the vagus nerves, keeping intact the hepatic and celiac branches.
 - Proximal gastric vagotomy (or Highly selective or parietal cell vagotomy):** This is designed to denervate the acid secretory part of the stomach, keeping the vagal supply to the alkali secreting gastric antrum and other abdominal viscera intact. The nerves of Latarjet to the pylorus are left intact; thus gastric emptying is unaffected and drainage procedure is not required.



Figs. 22.9A to C: Types of vagotomy. (A) Highly selective vagotomy, (B) Selective vagotomy with pyloroplasty, (C) Truncal vagotomy with gastrojejunostomy

COMPLICATIONS AFTER GASTRIC OPERATIONS

Early	Remote	Post-gastrectomy syndromes
<ul style="list-style-type: none"> Hemorrhage from anastomotic line Paralytic ileus Steatorrhoea Duodenal fistula Acute postoperative pancreatitis 	<ul style="list-style-type: none"> Recurrent ulcer Post-gastrectomy syndromes Gastrojejunocolic fistula Intestinal obstruction Pulmonary TB Anemia Osteomalacia and osteoporosis Ca in remnant Gallstones 	<ul style="list-style-type: none"> Weight loss Diarrhoea (MC after truncal vagotomy) Anemia (iron deficiency, megaloblastic) Vitamin B, Calcium deficiency, Vitamin D deficiency

Relevant points about Complications of Gastric Operations

- Duodenal fistula ('blow-out'):** Is an uncommon but serious complication of **Billroth II** gastrectomy with maximal incidence about the **fourth day** ("II X 2 = Four!")
- Recurrent ulceration:** This may be a true anastomotic ulcer or ulcer in gastric remnant. Symptoms are severe, persistent, **burning epigastric pain** worse within a few minutes of taking food. H2 blockers needed to heal the ulcer.
- Gastrojejunocolic fistula:** Is a complication of gastrojejunal ulcer and **more often follows simple gastroenterostomy** than partial gastrectomy.
- Afferent loop syndromes:**
 - **Bacterial overgrowth in the afferent limb** secondary to stasis; postprandial abdominal pain, bloating, and diarrhea with concomitant malabsorption of fats and vitamin B12.
 - Second type: **severe abdominal pain and bloating** that occur 20-60 minutes after meals. Pain is often followed by nausea and vomiting of bile-containing material. The pain and bloating may improve after emesis.

Postcibal ('Dumping' Syndromes)

- 'Early dumping':** MC after **Billroth II**, epigastric fullness, sweating, light headedness, tachycardia, colic, **immediately after meals (in 15-30 minutes)**, due to **rapid emptying of hyperosmolar gastric contents** into the small intestine, resulting in a fluid shift into the gut lumen with plasma volume contraction and acute intestinal distention.

- 'Late dumping': 90 min to 3 h after meals; aggravated by exercise; vasomotor symptoms (light-headedness, diaphoresis, palpitations, tachycardia, and syncope) predominate during this phase; late dumping is thought to be secondary to hypoglycemia from excessive insulin release.
- Treatment: Both problems improve naturally with time. Dietary measures are such as taking more protein and less of milk and carbohydrate (glucose); frequent small meals; limitation of liquids at mealtime. In severe cases symptoms may improve with octreotide.

Electrolyte changes in pyloric stenosis

- Hyponatremia
- Hypokalemia
- Hypochloremia
- Hypomagnesemia
- Metabolic alkalosis
- Paradoxic aciduria

PEPTIC ULCER DRUGS

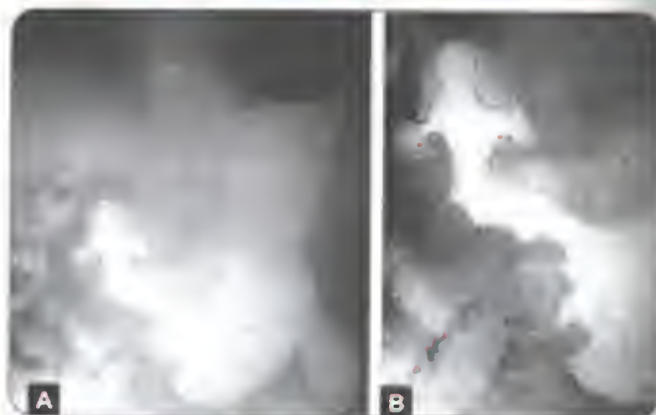
- These have been discussed in pharmacology chapter (Pg 338).

GASTRIC VOLVULUS (ROTATION)

- If the stomach twists, the classical triad of gastro-oesophageal obstruction may occur — Borchardt's triad:
 - Violent ineffective vomiting
 - Acute epigastric pain and
 - Failure to pass a nasogastric tube
- Risk factors are pyloric stenosis, congenital bands, paraesophageal hernia.

Miscellaneous Gastric Conditions

- Hair-ball of the stomach (Rapunzel syndrome): Trichobezoar occurs almost exclusively in female psychiatric cases; maybe a/w alopecia, abdominal pain and crepitus. Treatment is removal by gastrotomy.
- Hourglass stomach: MC in women, is usually silent, and is due to cicatricial contracture around a saddle shaped, lesser-curve ulcer.
- "Tea-pot" stomach or "handbag" stomach is due to cicatrization around a long-standing gastric ulcer often causing shortening of the lesser curvature.
- Secondary diverticula of the duodenum occur in the first part of the duodenum and are the result of scarring following duodenal ulceration seen as "trifoliate duodenum" on radiographs.
- Gossypiboma: An infrequent surgical complication, is a mass lesion due to a retained surgical sponge surrounded by foreign-body reaction.
- Chronic duodenal ileus (Wilkie's syndrome): Superior mesenteric artery syndrome.



Figs. 22.10A and B: Barium meal picture showing trifoliate duodenum as secondary diverticulum due to chronic duodenal ulcer

MENETRIER'S DISEASE (HYPERTROPHIC GASTRITIS)

- Giant hypertrophy of gastric rugae prominently in body and fundus.
- High, normal or low acid secretion.
- Excessive loss of protein from the thickened mucosa into the gut → hypoproteinemia (hypoalbuminemia) and edema.
- Diarrhea, anorexia, weight loss, skin rash and chronic blood loss may also occur.
- MC symptom is epigastric pain.
- Histologically, massive foveolar hyperplasia (hyperplasia of surface and glandular mucous cells) is noted.
- Etiology: Altered expression of TNF α .
- Medical treatment: Antacids, atropine (for protein leak).
- Increased risk of adenocarcinoma of stomach in adults with Menetrier's disease.

ZOLLINGER-ELLISON SYNDROME (ZES)

- ZES consists of severe peptic ulcers secondary to gastric acid hypersecretion due to unregulated gastrin release from a non- β -cell endocrine tumor (gastrinoma).
- Age affected = 30-50 years
- Etiology: Gastrinomas are classified into sporadic tumors (MC) and those a/w multiple endocrine neoplasia (MEN) type I.
- Location: Over 80% of these tumors are found within the hypothetical gastrinoma triangle — Psaros triangle (confluence of the cystic and common bile ducts superiorly, junction of the second and third portions of the duodenum inferiorly, and junction of the neck and body of the pancreas medially).

- MC site is proximal duodenal wall, next MC is pancreatic head; other sites are stomach, bones, ovaries, heart, liver and lymph nodes.

Clinically

- Peptic ulcers, usually solitary and located in the duodenal bulb.
- Gastric acid hypersecretion can cause direct intestinal mucosal injury and pancreatic enzyme inactivation, resulting in diarrhea, steatorrhea, and weight loss; nasogastric aspiration of stomach acid stops the diarrhea.

Suspect ZES when

- Increased fasting gastrin levels are a/w ulcers refractory to standard therapies
- Giant ulcers (> 2 cm)
- Ulcers located distal to the duodenal bulb (post bulbular ulcer), multiple duodenal ulcers
- Frequent ulcer recurrences
- Ulcers associated with diarrhea
- Ulcers occurring after ulcer surgery
- Patients with ulcer complications
- Patients with hypercalcemia or family histories of ulcers (suggesting MEN 1)
- Ulcers occurring in absence of H pylori and NSAIDs usage

Laboratory Findings

- Most sensitive and specific test: Increased fasting serum gastrin concentration (> 150 pg/ml).
- Gastric acid hypersecretion is present (pH < 3.0)
- IV secretin produces a rise in serum gastrin of over 200 pg/ml within 2-30 minutes.

Imaging

- Somatostatin Receptor Scintigraphy has a sensitivity (> 80%) for tumor detection that exceeds all other imaging studies combined.
- In patients with negative SRS, endoscopic ultrasonography (EUS) may be useful to detect small gastrinomas in the duodenal wall, pancreas, or peripancreatic lymph nodes.

Treatment

- Proton pump inhibitors are the treatment of choice.

EXTRA EDGE

- Gastrinoma triangle (Psaros triangle): 90% of gastrinomas are found here.

Linitis Plastica

- Diffuse fibrous proliferation of the submucous connective tissue of the stomach, resulting in thickening and fibrosis so that the stomach is constricted, inelastic, and rigid (like a leather bottle).

Differential diagnosis of linitis plastica

Neoplastic	Inflammatory
<ul style="list-style-type: none"> • Gastric carcinoma • Metastases – breast particularly • Lymphoma • Carcinoma of the pancreas – local invasion. 	<ul style="list-style-type: none"> • Boeck's sarcoid of the stomach, • Granulomata – TB, Crohn's disease • Radiotherapy • Corrosives • Eosinophilic gastroenteritis • Secondary syphilis

BARIATRIC SURGERY

- A.k.a Gastric Surgery for Morbid Obesity
- Done in patients with a BMI > 40 kg/m² (morbid obesity) or > 35 kg/m² (when a/w DM/HTN).
- Restrictive operations:
 - Laparoscopic adjustable silicone gastric banding (LASGB) – least risky procedure.
 - Laparoscopic Sleeve gastrectomy
- Restrictive-malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption:
 - Roux-en-Y gastric bypass: RYGB is the MC performed and accepted bypass procedure.
 - Biliopancreatic diversion (BPD) with/without duodenal switch — most effective type for weight loss, BUT highest perioperative mortality. Has highest incidence of resolution of diabetes and dyslipidemia.

UPPER GI BLEEDING

- MC cause of upper GI bleeding is duodenal ulcers.
- Rockall risk score and Blatchford risk score are pre-endoscopy scores used for risk stratification in upper GI bleeding.
- Dieulafoy's lesion: Also called persistent caliber artery, is a large-caliber arteriole that runs immediately beneath the gastrointestinal mucosa and bleeds through a pinpoint mucosal erosion. It is a gastric arterial venous malformation. It is seen MC on the lesser curvature of the proximal stomach, causes impressive arterial hemorrhage.

EXTRA EDGE

- Diverticulosis is the MC cause of acute lower GI bleeding.

TYPHOID

- Surgical complications of typhoid:
 - Paralytic Ileus
 - Intestinal hemorrhage
 - Perforation
 - Cholecystitis
- Perforation** of a typhoid ulcer usually occurs during the **third week**; the ulcer is **parallel to the long axis** of the gut and is usually situated in the **distal ileum**.

TUBERCULOSIS OF THE INTESTINE

- TB, like Crohn's disease, can affect any part of the GIT from the mouth to the anus.
- The sites affected most often are the **ileum, proximal colon and peritoneum**. There are two principal presentations.

Ulcerative TB

- This is secondary to pulmonary TB and arises as a result of swallowing tubercle bacilli.
- Multiple ulcers, lying transversely, develop in the terminal ileum and the overlying serosa is thickened, reddened and covered in tubercles.
- Patients typically present with diarrhea and weight loss.
- A regular course of ATT leads to cure

Hyperplastic TB

- This is caused by the ingestion of Mycobacterium tuberculosis by patients with a high resistance to the organism.
- The infection MC occurs in the ileocecal region
- Patients usually present with attacks of **abdominal pain** and **intermittent diarrhea**
- A barium follow-through or small bowel enema will show a long narrow filling defect in the terminal ileum (see radiodiagnosis chapter for radiological signs of ileocecal TB) (Pg 1180).
- Where obstruction is present, **surgery** with **ileocecal resection** is often required.

INTESTINAL DIVERTICULA

- Diverticula can occur anywhere from the esophagus to the recto-sigmoid junction (but NOT usually in the rectum).
- Congenital**: All three coats of the bowel are present in the wall of the diverticulum, e.g. Meckel's diverticulum.
- Acquired**: There is **NO muscularis layer** present in the diverticulum, e.g. sigmoid diverticula.
- Ilejunal** diverticula: Arise from the **mesenteric side of the bowel** as a result of mucosal herniation at the point

of entry of the blood vessels most often asymptomatic and discovered incidentally on imaging.

- Meckel's diverticulum**: See pediatrics chapter
- Diverticulosis of **large intestine**: MC in **sigmoid colon** (BUT in South East Asia right sided diverticula are more common). Usually asymptomatic but complications of diverticula are:
 - Pain and inflammation (**Diverticulitis**): characteristically presents with **fever, anorexia, left lower quadrant abdominal pain** and **obstipation**. The diagnosis of diverticulitis is best made on **CT scan**.
 - Hinchey classification** is for complications of diverticulitis.
 - Hartmann's procedure** is the safest option in emergency surgery.
 - Other complications are perforation, abscess, hemorrhage, fistula formation, intestinal obstruction.

MESENTERIC ISCHEMIA

- MC affects **superior mesenteric** vessels; **emboli are commoner** than thrombosis.
- Emboli originate from the **heart MC**.
- Acute mesenteric ischemia** presents with **severe acute, non-remitting abdominal pain (abdominal anginal)** strikingly out of proportion to the physical findings in a patient with **atrial fibrillation** or **atherosclerosis**.
- Nausea and vomiting, transient diarrhea and bloody stools may be present.
- A **high white cell count, lactic acidosis, hypotension (shock)** may aid in the diagnosis.
- A **mesenteric duplex scan (i.e. ultrasound can) demonstrating a high peak velocity of flow in the superior mesenteric artery (SMA)** is associated with an ~80% positive predictive value of mesenteric ischemia. More significantly, a negative duplex scan virtually precludes the diagnosis of mesenteric ischemia.
- Gold standard test** is laparotomy.
- Treat with surgical resection of infarcted bowel (**enterectomy**) and **anticoagulation**.

Abdominal X-ray in mesenteric Ischemia

- Earliest features include **bowel-wall edema, known as 'thumbprinting'**.
- If the ischemia progresses, **air can be seen within the bowel wall (pneumatosis intestinalis)** and within the portal venous system.
- Presence of **gas bubbles within the mesenteric veins** is **pathognomonic**.

ANGIODYSPLASIA

- A.k.a **angiomas, haemangiomas** and **artriovenous malformations**.

- This is a **vascular malformation** occurring particularly in the **ascending colon and caecum of elderly patients** (over 60 years).
- Causes **hemorrhage from the colon**; maybe subtle bleeds leading to anemia or maybe brisk bleeds leading to **melen** and rectal bleeds.
- Heyde's syndrome** = Angiodysplasia + aortic stenosis.
- Colonoscopic cauterization** maybe necessary.

ISCHEMIC COLITIS

- Ischemic colitis maybe due to embolism (very severe presentation) or due to thrombosis. Leads to deprivation of blood to colon.
- MC in the **splenic flexure**, whose blood supply is particularly tenuous.
- Marston classification**: Gangrenous, transient and stricturing forms; only stricturing forms cause obstruction.
- Abdominal X-ray may show **thumb printing**.
- Resuscitation and laparotomy** are required with resection of gangrenous bowel and exteriorisation of the bowel.

KEY POINTS ABOUT STOMAS

- May be **colostomy or ileostomy**; May be **temporary or permanent**.
- Temporary or defunctioning stomas are usually fashioned as **loop stomas**.

Ileostomy	Colostomy
Ileostomy is spouted	Colostomy is flush
Ileostomy effluent is usually liquid	Colostomy effluent is usually solid
Usually sited in the right iliac fossa	Usually sited in the left iliac fossa
Ileostomy patients are more likely to develop fluid and electrolyte problems	

Principles of management of enterocutaneous fistulae ("SNAP")

- S**, elimination of Sepsis and skin protection
- N**, Nutrition – a period of parenteral nutrition may be required
- A**, Anatomical assessment
- P**, definitive Planned surgery

INTESTINAL OBSTRUCTION**Types of Intestinal Obstruction**

- Dynamic**, in which peristalsis is working against a mechanical obstruction. It may occur in an acute or a chronic form — see etiology in box below.

- Adynamic**, in which there is no mechanical obstruction; peristalsis is absent or inadequate (e.g. **paralytic ileus** or **pseudo-obstruction**).

Causes of Dynamic intestinal obstruction

- Extramural**
 - Bands/**adhesions** (**MC Cause** -40%)
 - Hernia
- Intramural**
 - Stricture
 - Malignancy
 - Intussusception
 - Volvulus
- Intraluminal**
 - Fecal impaction
 - Foreign bodies
 - Bezoars
 - Gallstones

Strangulation

- The consequences of intestinal obstruction are not immediately life-threatening **unless** there is **superimposed strangulation**. When strangulation occurs, the **blood supply is compromised** and the **bowel becomes ischemic**.
- Clinical features of strangulation: **Constant, severe pain; Tenderness with rigidity** and peritonism; **Shock**.

Causes of strangulation

- Direct pressure on the bowel wall**
 - Hernial orifices
 - Adhesions/bands
- Interrupted mesenteric blood flow**
 - Volvulus
 - Intussusception
- Increased intraluminal pressure**
 - Closed-loop obstruction (classically seen in the presence of a malignant stricture of the colon with a competent ileocecal valve)

Internal Hernia

- Internal herniation occurs when a **portion of the small intestine** becomes **entrapped in one of the retroperitoneal fossae** or in a congenital mesenteric defect. The following are potential sites of internal herniation (all are rare):
 - The foramen of Winslow;
 - A defect in the mesentery;
 - A defect in the transverse mesocolon;
 - Defects in the broad ligament;
 - Congenital or acquired diaphragmatic hernia;

- Duodenal retroperitoneal fossae – left paraduodenal and right duodenojejunal;
- Caecal/appendiceal retroperitoneal fossae – superior, inferior and retrocaecal;
- Intersigmoid fossa.

Gallstone Ileus

- Gallstone causing intestinal obstruction is MC in the elderly secondary to erosion of a large gallstone directly through the gall bladder into the duodenum.
- Classically, there is impaction about **60 cm proximal to the ileocecal valve**.
- The patient may have recurrent attacks as the obstruction is frequently incomplete or relapsing as a result of a **ball-valve** effect.
- **Rigler's triad**: Characteristic radiological sign of gallstone ileus comprising:
 - Small bowel obstruction,
 - Pneumobilia and
 - an atypical mineral shadow on radiographs of the abdomen.
- The presence of *two of these radiological signs* has been considered **pathognomonic of gallstone ileus** and is encountered in 40–50 per cent of the cases.
- If the *gallstone is faceted*, a careful check for *other enteric stones* should be made.

Volvulus

- May involve the *small intestine, caecum or sigmoid colon*; *neonatal midgut volvulus* secondary to midgut malrotation is life-threatening.
- **MC** spontaneous type in **adults** is **sigmoid volvulus**
- Sigmoid volvulus can be relieved by *decompression per anum*.
- **Surgery** is required to prevent or relieve ischemia.

Clinical Features of Intestinal obstruction

- In **high small bowel** obstruction:
 - **Vomiting** occurs *early*, is profuse and causes rapid dehydration.
 - *Distension* is *minimal* with little evidence of dilated small bowel loops on abdominal x-ray.
- In **low small bowel** obstruction:
 - **Pain** is predominant with central distension.
 - Vomiting is delayed.
 - Multiple dilated small bowel loops are seen on radiography.
- In **large bowel obstruction**:
 - **Distension** is pronounced.
 - Pain is less severe and vomiting and dehydration are later features.
 - The colon proximal to the obstruction is distended on abdominal radiography.
 - The small bowel will be dilated if the ileocecal valve is incompetent.

Cardinal Clinical Features of Acute Obstruction

- **Abdominal pain**:
 - Pain is **first symptom**; **sudden, severe** and **colicky**; pain *coincides with increased peristaltic activity*; severe continuous persisting pain suggests *strangulation*.
- **Distension**:
 - *Varies* with the level of obstruction as mentioned in box above.
- **Vomiting**:
 - The more distal the obstruction, the longer the interval between the onset of symptoms and the appearance of nausea and vomiting as mentioned in box above.
- **Absolute constipation**:
 - This may be **absolute** (i.e. neither faeces nor flatus is passed) or **relative** (where *only flatus* is passed).
 - The administration of enemas should be avoided in cases of suspected obstruction.
 - The rule that absolute constipation is present in intestinal obstruction **does NOT apply in**:
 - Richter's hernia
 - Gallstone ileus
 - Mesenteric vascular occlusion
 - Functional obstruction associated with pelvic abscess
 - All cases of partial obstruction (in which diarrhea may occur).
- **Late manifestations** of intestinal obstruction: Dehydration, oliguria, hypovolaemic shock, pyrexia, septicaemia, respiratory embarrassment and peritonism.

Radiological Features of Obstruction (on Plain X-ray)

- Erect abdominal films are no longer routinely obtained and the radiological diagnosis is based on a **supine abdominal film**.
- The obstructed small bowel is characterized by **straight segments** that are generally **central and lie transversely**.
- **No/minimal gas** is seen in the colon
- The jejunum is characterised by its **valvulae conniventes**, which completely pass across the width of the bowel and are regularly spaced, giving a '**concertina**' or **step-ladder effect**.
- Ileum- Distal ileum has been described by **Wangensteen** as **featureless**.
- Caecum — A distended caecum is shown by a rounded **gas shadow in the right iliac fossa**.
- Large bowel, except for the caecum, shows **haustal folds**, which, unlike valvulae conniventes, are **spaced**

irregularly, do not cross the whole diameter of the bowel and do not have indentations placed opposite one another.

Treatment of Acute Intestinal Obstruction

- Gastrointestinal drainage via a **nasogastric tube**:
- Fluid and **electrolyte replacement**.
- Relief of obstruction: **Surgical treatment** is necessary for most cases of intestinal obstruction but should be delayed until resuscitation is complete, provided there is no sign of strangulation or evidence of closed-loop obstruction.
- Indications for **early surgical intervention**:
 - Obstructed external hernia
 - Clinical features suspicious of intestinal strangulation
 - Obstruction in a 'virgin' abdomen.

Pseudo-obstruction

- This condition describes an obstruction, usually of the colon, that occurs in the absence of a mechanical cause or acute intra abdominal disease.
- It is a/w a variety of syndromes in which there is an underlying neuropathy and/or myopathy and a range of other factors- see box below.

Causes of pseudo-obstruction

- Metabolic: Diabetes; Hypokalemia; Uraemia; Myxoedema; Intermittent porphyria.
- Severe trauma (especially to the lumbar spine and pelvis).
- Shock: Burns; Myocardial infarction; Stroke; Idiopathic; Septicaemia; Postoperative (ex: fractured neck of femur)
- Retroperitoneal irritation: Blood, Urine; Enzymes (pancreatitis); Tumor.
- Drugs: Tricyclic antidepressants; Phenothiazines; Laxatives.
- Secondary GIT involvement: Scleroderma; Chagas' disease.

RECTAL PROLAPSE

Mucosal Prolapse

- The **mucous membrane and submucosa** of the rectum protrude outside the anus for approximately 1–4 cm
- **More common** in **infants, children**.
- In **adults** it is often a/w **third-degree hemorrhoids**. In the female, a torn perineum, and in the male straining from urethral obstruction, predispose to mucosal prolapse.
- **Prolapsed mucous membrane is pink**; prolapsed internal hemorrhoids are **plum colored** and more pedunculated.
- Treatment- In infants and children:
 - Digital repositioning

- Submucosal injections of 5% phenol in almond oil under GA
- Occasionally surgery
- In adults
 - Submucosal injection as above or excision of prolapsed mucosa.

Full Thickness Prolapse

- A.k.a **proctodia**; **Less common** than the mucosal prolapse.
- **M:F = 6:1**; In women it may be a/w *prolapse of uterus*
- **Complete prolapse** is rare in children BUT can occur in the **elderly**.
- The protrusion consists of **ALL layers of the rectal wall** and is usually a/w a weak pelvic floor.
- The process **starts with the anterior wall** of the rectum.
- It is more than 4 cm and commonly as much as 10–15 cm in length.
- Any prolapse *over 5 cm in length* contains anteriorly between its layers a *pouch of peritoneum*.
- In adults it is a/w *fecal incontinence* in 50% cases.
- **Surgery** is the treatment of choice. The operation is performed either via the perineum (*more commonly*) or via the abdomen (**abdominal rectopexy**).
- Perineal procedures are **Thiersch's** operation, **Delorme's** operation and **Altemeier's** procedure.

Causes of Infective proctitis

- *Clostridium difficile*
- Amoebic dysentery
- Bacillary dysentery
- AIDS
- LGV
- Gonococcal proctitis
- Tuberculous proctitis
- **Strawberry lesion** of the rectosigmoid (due to *Spirocheta vincenti* and *Bacillus fusiformis*)
- Rectal **bilharziasis** (*S.mansonii*).

CONDITIONS OF THE ANUS

- **Imperforate anus** is classified as being high or low depending on the site of the rectal termination in relation to the pelvic floor:
 - Low defects: Relatively easy to correct, but prone to constipation.
 - High defects: More difficult to correct and prone to fecal incontinence.
- A **post-anal dimple** (**synonym: fovea caecygea**) is a dimple in the skin beneath the tip of the coccyx, sometimes amounting to a short blind pit.
- **Pilonidal sinus** has been called **Jeep disease**.

Anal Fissure

- Maybe Acute or chronic.
- Ischemic ulcer in the **posterior midline (MC)** of the anal canal.
- Clinically: **Pain** on defecation; **Bright-red** bleeding; Mucous discharge; Constipation.
- Treatment of an anal fissure:
 - Conservative initially, consisting of stool-bulking agents and softeners, and chemical agents in the form of ointments designed to relax the anal sphincter and improve blood flow.
 - Surgery if above fails, consisting of lateral internal sphincterotomy or anal advancement flap.

Fistula in Ano

- **Park's classification** is used to classify anal fistulas.
- **Intersphincteric** type is MC.
- **Goodsall's rule** is applied to find the site of the internal opening according to the position of the external opening.
- **MRI is the gold standard** for fistula imaging.
- Treatment is **surgical** - fistulotomy, fistulectomy or use of setons.

Internal Hemorrhoids

- **Internal hemorrhoids** (Greek: Haïma, blood; rhoos, flowing; synonym: piles, Latin: pila, a ball) are **symptomatic anal cushions** and characteristically lie in the **3, 7 and 11 o'clock** positions
- Symptoms of hemorrhoids: bright-red, painless, bleeding mucous discharge, prolapse, pain only on prolapse.
- Four degrees of hemorrhoids:
 - First degree—bleed only, no prolapse
 - Second degree—prolapse, but reduce spontaneously
 - Third degree—prolapse and have to be manually reduced
 - Fourth degree—permanently prolapsed.
- Treatment of hemorrhoids:
 - Symptomatic—advice about defecatory habits, stool softeners and bulking agents
 - Injection of sclerosant
 - Banding
 - Transanal hemorrhoidal dearterialisation/ haemorrhoidopexy
 - Hemorrhoidectomy.

External Hemorrhoids

- External hemorrhoids relate to **venous channels of the inferior hemorrhoidal plexus** deep in the skin surrounding the anal verge and are not true hemorrhoids.
- A **thrombosed external hemorrhoid** relates anatomically to the veins of the superficial or external hemor-

rhoidal plexus and is commonly termed a '**perianal haematoma**'.

- It presents as a sudden onset, **olive-shaped, painful blue subcutaneous swelling** at the anal margin and is usually consequent upon straining at stool, coughing or lifting a heavy weight.
- In the majority of cases, resolution or fibrosis occurs. Indeed, this condition has been called '**a 5-day, painful, self-curing lesion**' (Milligan).

HIGH YIELD POINTS

- **Capsule endoscopy:** A **pill sized (26 mm X 11 mm, 4 grams) capsule containing LED cameras transmits video images** via radiowaves to pads on the skin. Info is stored on a device worn on the belt. Normal activity can take place during the procedure; **Indication:** Assessment of **small bowel disease (especially Crohns)** after ruling out any strictures. The capsule takes 2 images/second; is swallowed after 12 hours of fasting and is passed out in the stool; capsule retention is the complication in 5% cases.
- Diseases called "**Captain of the men of death**" = **Carcinoma stomach** (Lord Moynihan labeled this) and **Streptococcal pneumonia** (Sir William Osler labeled this).
- **MC cause of dynamic intestinal obstruction is adhesions.**

ILEUS

- **Paralytic ileus** is defined as a state in which there is failure of transmission of peristaltic waves secondary to neuromuscular failure [i.e., in the myenteric (Auerbach's) and submucosa (Meissner's) plexuses].
- The resultant stasis leads to accumulation of fluid and gas within the bowel, with associated distension, vomiting, absence of bowel sounds and absolute constipation.
 - Varieties:
 - **Postoperative ileus:** Self limiting in **24-72 hours**; maybe prolonged in presence of **hypoproteinemia** or metabolic abnormality.
 - **Infection:** intra-abdominal sepsis.
 - **Reflex ileus:** following **fractures of the spine or ribs, retroperitoneal hemorrhage** or even the application of a plaster jacket.
 - **Metabolic:** uremia, hypokalemia.

PEDIATRIC GIT SURGICAL CONDITIONS

This has been covered in **pediatrics chapter** and includes the following topics (Pg 682):

1. Congenital diaphragmatic hernia
2. Tracheo-esophageal fistula

3. Infantile hypertrophic pyloric stenosis
4. Duodenal atresia
5. Necrotising enterocolitis
6. Intussusception
7. Hirschsprung's disease
8. Volvulus
9. Meconium ileus

APPENDICITIS

Important Appendix Points

- The vermiform appendix is present only in **humans**, certain **anthropoid apes** and the **wombat**.
- **MC position = Retrocecal**
- 2nd MC = Pelvic
- **Least Common position = Postileal**
- **Appendicular artery** is a branch of **ileocolic artery**.
- **Accessory appendicular artery** (of Seshachalam) may be present.
- **Wallbridge classification** is used for **duplication of appendix**.

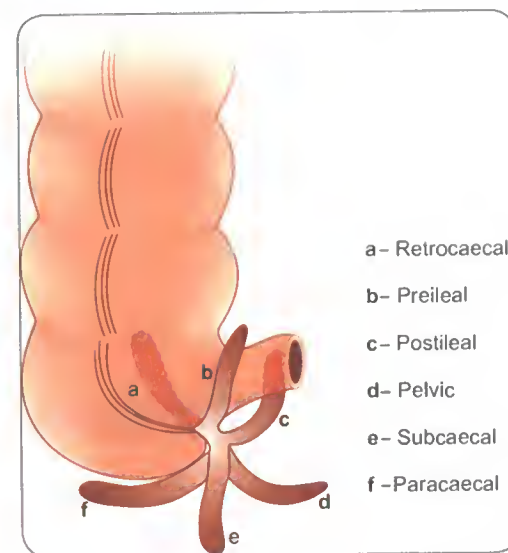


Fig. 22.11: Different anatomical positions of the appendix

Risk Factors for Perforation of the Appendix

- Extremes of age
- Immunosuppression
- Diabetes mellitus
- Faecolith obstruction
- Pelvic appendix
- Previous abdominal surgery

Symptoms of Appendicitis

- Periumbilical colic
- Pain shifting to the right iliac fossa

- Anorexia
- Nausea

Signs in Appendicitis

- Pyrexia
- Localised tenderness in the right iliac fossa
- Muscle guarding
- Rebound tenderness

Special Features according to Position of the Appendix

- **Retrocaecal:**
 - Rigidity is often absent, and even application of deep pressure may fail to elicit tenderness ("**silent appendix**")
 - However, **deep tenderness** is often present in the loin, and **rigidity of the quadratus lumborum** may be in evidence.
 - **Psoas spasm**, due to the inflamed appendix being in contact with that muscle, may be sufficient to cause **flexion of the hip joint**.
- **Pelvic:**
 - An inflamed appendix in contact with the bladder may cause **frequency of micturition**; MC in **children**.
 - **Tenderness** present in the rectovesical pouch (pouch of **Douglas**), especially on the **right** side.
- **Postileal:**
 - Pain may **NOT shift**, **diarrhoea** is a feature and **marked retching** may occur.

Special Features of Acute Appendicitis according to Age

- **In infants (< 36 months age):**
 - Very **rare** but has **high perforation** rates and **high mortality**.
- **In children:**
 - Here localisation is **NOT** present and hence **perforation and peritonitis occurs early**;
 - It requires **early surgery**
 - **Inv. of choice** in children is **Ultrasonography**.
 - Severe **vomiting** and complete **aversion to food**
- **In elderly:**
 - **Gangrene and perforation** occur much **more frequently in elderly**.
- **In obese:**
 - Obesity can obscure all the local signs of acute appendicitis.
 - **Large midline abdominal incision** maybe required.
 - **Laparoscopy** is particularly useful in the obese as it may **obviate the need for a large abdominal incision**.

- **In pregnancy:**
 - Appendicitis is the *MC extrauterine acute abdominal condition in pregnancy*
 - However, the cardinal feature of appendicitis in pregnancy, **pain in the right lower quadrant** of the abdomen.

Signs in Appendicitis (Fig. 22.1)

1. **Pointing sign:** The patient is asked to point to where the pain began and where it moved.

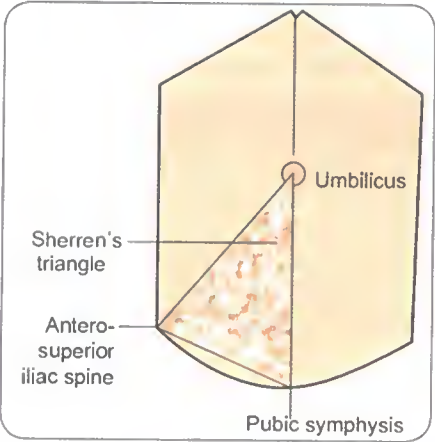


Fig. 22.12: Sherren's triangle. It is area of hyperaesthesia found in acute appendicitis between anterosuperior iliac spine; umbilicus and pubic symphysis

2. **Rovsing's sign:** Pain at McBurney's point induced in cases of appendicitis, by pressure exerted over the descending colon.
3. **Psoas sign:** Occasionally, an inflamed appendix lies on the psoas muscle, and the patient, often a young adult, will lie with the right hip flexed for pain relief.
4. **Obturator test; Zachary Cope:** Spasm of the obturator internus is sometimes demonstrable when the hip is flexed and internally rotated. If an inflamed appendix is in contact with the obturator internus, this manoeuvre will cause pain in the hypogastrium
5. **Aaron's sign:** A referred pain or feeling of distress in the epigastrium or precordial region, on continuous firm pressure over McBurney's point, in acute appendicitis.
6. **Bastedo's sign:** Pain and tenderness in the right iliac fossa on inflation of the colon with air, in cases of chronic appendicitis.
7. **Blumberg's sign (release sign):** Tenderness and rebound tenderness at McBurney's point.
8. **Dumphy's cough tenderness sign**
9. **Dieulafoy's triad:** Tenderness, muscular contraction and skin hyperaesthesia at McBurneys point in appendicitis.

10. **Ten horn sign:** Marked tenderness upon manual tension applied to right spermatic cord in acute appendicitis.
11. **Baldwing's test:** In retrocecal appendix; when legs are lifted off the bed with knee extended, patients c/o pain while pressing on the flanks.
12. **Bapat Bed shaking test**
13. **Markle's sign (Heel drop test):** Pain in the Rt.lower quadrant on dropping from standing on toes to heels
14. **Caecal bar sign:** Appearance of inflammatory soft tissue at the base of the appendix, separating the appendix from the contrast-filled cecum
15. **Arrowhead sign:** Focal caecal thickening centered on the appendiceal orifice; the contrast material in the cecal lumen assumes an arrowhead configuration, pointing at the appendix.
16. **Murphy's triad** = Pain, vomiting, temperature.
17. **Bassler's sign:** Sharp pain created by compressing appendix between abdominal wall and iliacus in chronic appendicitis.

Diagnosis

- Diagnosis is **mainly clinical**; however, a decision to operate based on clinical suspicion alone can lead to the removal of a normal appendix in 15-30 percent of cases.
- **Ultrasound** is investigation of choice in children with acute appendicitis.
- **Contrast-enhanced CT scan** is most useful in older patients.

Alvarado scoring system (M-A-N-T-R-E-L-S)

- Symptoms: **M**igration; **A**norexia; **N**ausea-vomiting
 - Signs: **T**enderness in right iliac fossa; **R**ebound pain; **E**levated temperature > 37.3 deg C)
 - Labs: **L**eukocytosis; **S**hift to the left
- Score of 7 = requires operation
Score of 5-6 = observation
Score of 4 = appendicitis unlikely

Other Scoring Systems for Appendicitis

1. Tzanakis score (U/S with clinical and lab findings)
2. Appendicitis Inflammatory Response Score
3. Ohmann score
4. Lintula score
5. Pediatric Appendicitis score (Samuel score)
6. Ripasa scoring system
7. Anderson scoring system.

APPENDICECTOMY

History

- **FIRST appendicectomy** was performed by **Claudius Amyand** - he successfully removed an acutely inflamed appendix from the hernial sac of a boy in 1736
- **Amyand's hernia** is a rare form of inguinal hernia in which the vermiform appendix is located within the hernial sac!
- **Lawson Tait:** The first surgeon to perform deliberate appendicectomy for acute appendicitis in May 1880.
- **Thomas Morton:** was the first to diagnose appendicitis, drain the abscess and remove the appendix with recovery, publishing his findings in 1887.

Incisions for Appendicectomy

Incision	Comments
Muscle-splitting incision	
1. Gridiron (McBurney's or MacArthur's)	
2. Lanz (interspinous) crease incision (a.k.a Modified McBurney, Rockey Davis or Bikini incision)	Cosmetically better
3. Right lower paramedian incision	When there is a doubt or diffuse peritonitis
Muscle-cutting incision	
1. Rutherford Morrison's	Muscles cut laterally upwards
2. Fowler-Weir	
3. Abbernethy's oblique iliac incision	

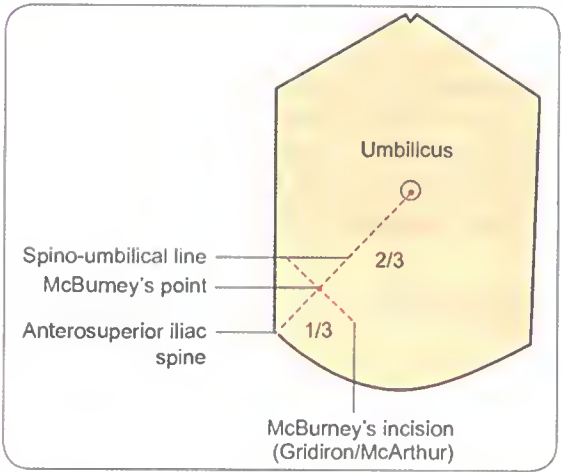


Fig. 22.13: McBurney's point is junction of lateral 1/3rd and medial 2/3rd of spino-umbilical line. McBurney's/Gridiron's/McArthur's incision is perpendicular to this line in this point

Appendix Mass

- If a mass is felt in appendicitis case and condition of the patient is satisfactory, it is preferable to adopt a conservative approach — **Ochsner-Sherren regimen**.
- Principle: This approach is based on the assumption, that the inflammatory process is already localised and that inadvertent surgery is difficult and may be dangerous. It may be impossible to find the appendix and, occasionally, a faecal fistula may form.
- A **contrast-enhanced CT** examination of the abdomen should be performed and anti-biotic therapy started.
- An **abscess**, if present, should be drained radiologically.
- **Temperature** and pulse rate should be recorded 4-hourly and a fluid balance record maintained.
- Clinical improvement is usually evident *within 24-48 hours*.
- Using this regimen, **approximately 90 percent of cases resolve** without incident.
- The great majority of patients will not develop recurrence, and it is **NO** longer considered necessary to remove the appendix after an interval of 6-8 weeks.
- **Criteria for stopping conservative treatment** of an appendix mass:
 - A rising pulse rate
 - Increasing or spreading abdominal pain
 - Increasing size of the mass.

Retroperitoneal Zones

- These zones are important from treatment point of view since upto 4 litres of blood can accumulate in retroperitoneal hematomas following trauma.

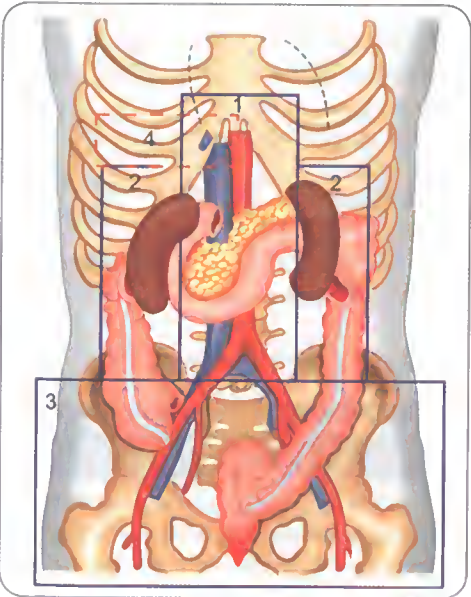


Fig. 22.14: Retroperitoneal zones

- As a general rule, routine exploration in **blunt trauma** should be considered **only for** pancreaticoduodenal hematomas (zone 1) since bleeding is from the aorta or inferior vena cava.
- But for penetrating trauma in any/all zones - they have to be explored.

Zone	Structures
1. (central)	Pancreaticoduodenal injuries, major vascular injury
2. (lateral)	Renal trauma, ureteric or colonic injury
3. (pelvic)	Pelvic fracture or ileofemoral vascular injury

HERNIA

Inguinal Region Anatomy

- The **superficial inguinal ring** is a **triangular aperture** in the **aponeurosis of the external oblique**, and lies **1.25 cm above the pubic tubercle**.
- The **deep inguinal ring** is a **U-shaped opening** in the **transversalis fascia**, 1.25 cm above the midinguinal point
- Inguinal canal**: In infants, the superficial and deep inguinal rings are almost superimposed and, the obliquity of the canal is only slight
- In adults, the **inguinal canal which is 3.75 cm** long, is directed downwards and medially, from the deep to the superficial inguinal ring.
- In the male the **inguinal canal transmits the spermatic cord**, the **ilioinguinal nerve**, the **genital branch of the genitofemoral nerve**. In the female the **round ligament** substitutes the **spermatic cord**.
- The **constituents of the spermatic cord** are:
 - The ductus (**vas**) deferens
 - Testicular** and **cremasteric** arteries, artery of ductus deferens
 - Pampiniform** plexus of veins
 - Lymph vessels from the testis
 - Genital branch of the genitofemoral nerve** and **sympathetic plexus** around the artery to ductus deferens
 - Remains of the processus vaginalis.

The coverings of the spermatic cord are (from within outwards)

- Internal spermatic fascia** derived from **fascia transversalis**
- Cremasteric fascia** made up of muscle loops constituting cremaster muscle, derived from the **internal oblique and transversus abdominis muscles**
- External spermatic fascia** derived from the **external oblique aponeurosis**

Boundaries of the Inguinal Canal

- Anteriorly**. External oblique aponeurosis. The conjoined muscle (mainly internal oblique) laterally.
- Posteriorly**. Inferior epigastric artery, fascia transversalis, conjoined tendon (internal oblique and transversus) medially.
- Superiorly**. Conjoined muscles (internal oblique and transversus)
- Inferiorly**: Inguinal ligament (Poupart's ligament)

Hesselbach's triangle

It is bounded:

- Medially by the lateral border of rectus abdominis,
- Laterally by the inferior epigastric artery, and
- Below by the inguinal ligament.

A direct inguinal hernia passes through this triangle.

Deep Ring Occlusion Test

- Impulse on coughing**, **groin swelling** and **reducibility** are features of **both direct and indirect** inguinal hernias.
- The **classic diagnostic point** to differentiate between the two is a **positive deep ring occlusion test**.
- In **deep ring occlusion test**: Patient is asked to lie down and the hernia is reduced. The position of deep inguinal ring is marked out. **The deep inguinal ring lies 1.25 cm above the mid inguinal point which is situated at the midpoint between anterior superior iliac spine and symphysis pubis**. The thumb is placed over the deep ring and patient is asked to cough. Look whether any cough impulse is seen medial to the deep ring. If no expansile impulse is seen in lying down position, patient is asked to stand with the deep ring occluded and is asked to cough again:
 - If no expansile impulse is seen on coughing, it suggests an **indirect hernia**.
 - If **expansile impulse is seen on coughing**, it suggests a **direct inguinal hernia**.

Nyhus Classification of Groin Hernia

- Type I**: Indirect inguinal hernia—internal inguinal ring normal (e.g. pediatric hernia)
- Type II**: Indirect inguinal hernia—internal inguinal ring dilated but posterior inguinal wall intact; inferior deep epigastric vessels not displaced.
- Type III**: Posterior wall defect:
 - III A: Direct inguinal hernia

- III B: Indirect inguinal hernia—internal inguinal ring dilated, medially encroaching on or destroying the transversalis fascia of Hesselbach's triangle (e.g. massive scrotal, sliding, or pantaloon hernia)
- III C: Femoral hernia
- Type IV**: Recurrent hernia
 - IV A: Direct
 - IV B: Indirect
 - IV C: Femoral
 - IV D: Combined.

EXTRA EDGE

Based upon its contents hernia maybe a omentocele (containing omentum) or enterocele (containing intestine).

- Omentocele**: NO gurgling heard during reduction; First part is easy to reduce but last part is almost IMPOSSIBLE to reduce.
- Enterocele**: reduces with Gurgle; first part maybe difficult to reduce BUT last part reduces easily.

Different Hernias

- Dual (Saddle bag or Pantaloon) hernia**—A type of direct hernia where there are **two sacs straddling the inferior epigastric artery**, one sac being medial and the other lateral to this vessel.
- Epigastric hernia**—fatty hernia of the line alba.
- Umbilical hernia (Exomphalos)**:
 - Exomphalos minor**—The sac is relatively small and to its summit is attached the umbilical cord. It is necessary only to twist the cord so as to reduce the contents of the cord and retain it by firm **strapping for 14 days**.
 - Exomphalos major**—Umbilical cord is attached to the inferior aspect of the swelling, which contains small and large intestine, and nearly always a portion of the liver. **Operation within the first few hours of life** is the treatment; otherwise the sac will burst.

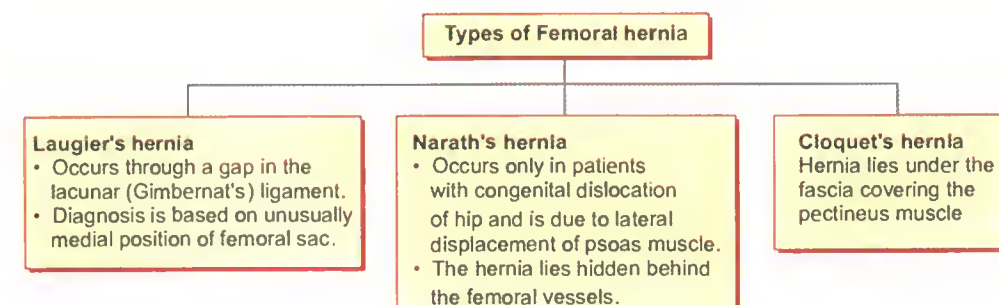
- Littre's hernia**—Hernial sac containing **Meckel's diverticulum**.
- Maydl's hernia**—(**hernia-in-W**). The strangulated loop of the W lies within the abdomen, thus **local tenderness over the hernia is not marked**.
- Paraumbilical hernia of adults** (supra or infraumbilical hernia)—**Mayo's operation** is done.
- Richter's hernia**—Hernial sac contains **a portion of the circumference of the intestine**.
- Sliding hernia (hernia-en-glissade)**—As a result of slipping of posterior parietal peritoneum on the retroperitoneal structures, the **posterior wall of the sac** is not formed of peritoneum alone, but by the **sigmoid colon and its mesentery on the left, the cecum on the right** and sometimes **on either side by a portion of the bladder**.

Surgeries for Femoral Hernia

- Lockwood's operation**: Low operation
- McEvedy operation**: High operation; Combined inguino-femoral approach

Rare External Hernias

- Interparietal (interstitial) hernia**—hernial sac passes **between the layers of anterior abdominal wall. Intermuscular (MC)** with the sac passing between external and internal oblique muscles.
- Spigelian hernia** is a variety of interparietal hernia occurring at the level of the **arcuate line**. A soft reducible mass may be felt below the umbilicus.
- Lumbar hernia**—most occur through the **inferior lumbar triangle of Petit**
- Obturator hernia**—passes through the obturator canal, more common in **women**.
- Gluteal hernia** passes through the greater sciatic foramen, either above or below the piriformis.
- Sciatic hernia** passes through the lesser sciatic foramen.



Other Named Hernias

Barth's hernia	Engagement of a loop of intestine between a persistent vitelline duct and the abdominal wall
Beclard's hernia	Through the opening for the saphenous vein
Holthouse hernia	Inguinal hernia with extension of loop of intestine along Paupart's ligament
Malgaigne's hernia	Infantile inguinal hernia prior to descent of testes
Rakitsky's hernia	Separation of muscular fibres of the bowel allowing protrusion of a sac of mucous membrane or of the peritoneum
Treitz hernia	duodenajejunal hernia
Velpeau's hernia	a femoral hernia where the intestine is in front of blood vessels
Gibbon's hernia	Hernia with hydrocele
Berger's hernia	Hernia into pouch of Douglas
Beclard's hernia	Femoral hernia through opening of saphenous vein
Amyand's hernia	Inguinal hernia containing appendix
Ogilvie's hernia	Hernia through the defect in conjoint tendon just lateral to where it inserts with the rectus sheath
Stammers hernia	Internal hernia occurring through window in the transverse mesocolon after retrocolic gastrojejunostomy
Petersen hernia	Hernia under Roux limb after Roux-en-Y

Basics of Hernia Surgery

- **Eduardo Bassini** is the '**father of hernia repair surgery!**'
- **Herniotomy and repair (herniorrhaphy)** consists of:
 - Excision of the hernial sac plus
 - Repair of the stretched transversalis fascia and
 - Further reinforcement of the posterior wall of the inguinal canal.
- (2) and (3) must be achieved without tension resulting in the wound and various techniques exist to achieve this, e.g. Shouldice operation, fascial flaps or mesh implants.
- During surgery, after dividing the superficial fasci and securing hemostasis, external oblique aponeurosis and the superficial inguinal ring are identified. The **external oblique aponeurosis is incised in the line of its fibres** and the structures beneath carefully separated from its

deep surface before completing through the superficial inguinal ring. In this way the **ilioinguinal nerve is safeguarded**.

- **Right inguinal hernia** is more common following a **grid iron (Mc Burney's)** incision for appendicectomy and is due to injury to the **iliohypogastric nerve**.
- **Polypropylene** suture is used in **hernia repair** because it is **synthetic monofilament dyed non absorbable** suture with **low tissue reaction** and **high tensile strength**.

Landmarks a/w Hernia Repair

Triangle of Doom

- By **vas deferens medially, spermatic vessels laterally** and **external iliac vessels inferiorly**.
- This triangle contains external iliac artery and vessels, the deep circumflex iliac vein, the genital branch of genitofemoral nerve and hidden by fascia the femoral nerve.
- **Staple should not be applied** in this triangle otherwise; chances of mortality are there if these great vessels are injured.

Triangle of pain

- **Spermatic vessel medially, the iliopectic tract laterally** and **inferiorly the inferior edge of skin incision**.
- This triangle contains lateral femoral cutaneous nerve and anterior femoral cutaneous nerve of thigh.
- **The staple in this area should be less** because nerve entrapment can cause neuralgia.

Circle of Death (corona mortis)

- Refers to vascular ring formed by the anastomosis of an **oberrant obturator artery (from infr epigastric artery)** with the **normal obturator artery arising from a branch of the internal iliac artery**. At the time of laparoscopic hernia if this vessel is torn both end of vessel can bleed profusely, because both arise from a major artery!

Athletic Pubalgia

- A.k.a **sportsman's hernia** or **sports hernia**, **Gilmore's groin** or **groin disruption**.
- Slips from rectus abdominis and adductor longus tendons decussate along the anterior aspect of symphysis pubis, contributing to the support of that articulation. A complex interplay among these structures contributes to the stability of the anterior pelvis. Injury to the rectus abdominis or adductor longus muscles and tendons leads to micro-instability and a sequence of events that culminates in chronic groin pain:
 - MC seen in men.

LIVER, GALL BLADDER AND PANCREAS

AMEBIC LIVER ABSCESS

- Extraintestinal infection by *E. histolytica* most often involves the **liver**; MC in **males**.
- **Amebic liver abscesses** are always preceded by intestinal colonization, which **may be asymptomatic**.
- Pathology.
- The necrotic contents of a liver abscess are classically described as **"anchovy paste pus,"** although the fluid is variable in color and is composed of **bacteriologically sterile granular debris** with few or no cells.
- Amebas, if seen, tend to be found near the capsule of the abscess.

Complications

- **Pleuropulmonary involvement** (rupture into lung) is the **MC complication**.
- A **hepatobronchial fistula** may cause cough productive of large amounts of necrotic material that may contain amebas. This dramatic complication carries a **good prognosis**.

Clinically

- **Fever, right-upper-quadrant pain**, which may be dull or pleuritic in nature and may radiate to the shoulder.
- Point tenderness over the liver and right-sided pleural effusion are common.
- Jaundice is **RARE**.
- **Abscess** more common in **right lobe**.

Treatment

- **Metronidazole** is the **drug of choice for amebic liver abscess**. More than **90% of patients respond dramatically to metronidazole therapy** with decreases in both pain and fever within 72 h.
- The **second-line** therapeutic agents are **emetine** and **chloroquine**.

Indications for aspiration of liver abscesses are:

- The need to rule out a pyogenic abscess, particularly in patients with multiple lesions;
- The lack of a clinical response in 3–5 days
- The threat of imminent rupture; and
- The need to prevent rupture of left lobe abscesses into the pericardium.
- There is **NO evidence** that aspiration, even of large abscesses (up to 10 cm), accelerates healing

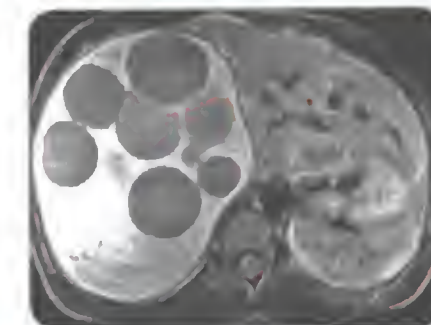


Fig. 22.15: Magnetic resonance image picture of multiple hydatid cyst of liver—MRI is very useful investigation in hydatid cyst of liver

HYDATID CYST

Etiopathology

- Caused by dog tapeworm, *Echinococcus granulosus*.
- **Definitive host: Dog**
- **Intermediate host: Humans, Sheep, Cattle.**
- Route of infection: GIT, oral route.
 - Outer **pericyst**: derived from compressed host organ tissues
 - Intermediate **ectocyst**: non-infective
 - Inner **endocyst**: i.e. germinal membrane and contains brood corpuscles with scolices; secretes hydatid fluid.

Clinically:

- **Liver is MC affected** (Lung is second MC)
- Presents as **enlarging painful mass in right upper quadrant** (due to stretching of liver capsule).
- Complication: **Rupture into biliary tree** causing **obstructive jaundice** or acute cholangitis.

Investigations:

- **Casoni's test**: Intradermal skin test
- ELISA and IHA: Specific tests
- **CT scan (best modality)** and ultrasound: space occupying lesion with smooth outline with septa.
- Hydatid fluid: Clear, sterile, **high specific gravity** (1.005–1.009)

Treatment:

- **Asymptomatic and inactive cysts**: leave alone and monitor by U/S.
- **Active cysts**: first treat with full course of **albendazole**
- Surgical procedures:
 - **PAIR** (Puncture, Aspiration, Injection, Reaspiration)
 - Pericystectomy with omentoplasty
 - Hepatic segmentectomy.

EXTRA EDGE

- Malignant hydatid disease is caused by *E. multilocularis* which is a benign disease and presents with multiple small cysts in both lobes of liver.

CLASSIFYING THE SEVERITY OF CHRONIC LIVER DISEASE

- Two prognostic models commonly used to assess the severity of chronic liver disease (cirrhosis) and perioperative risk are the
 - **Child-Turcotte-Pugh (CTP) Classification**
 - **Model for End-Stage Liver Disease (MELD) score.**
- The CTP classification has been modified from the original Child classification which was developed to predict mortality following shunt surgery in cirrhotic patients.
- The original Child's classification had 'nutrition' instead of 'prothrombin time'; 'nutrition' being graded as 'excellent, good and poor'. However, the modified Child's classification has prothrombin time (an NOT nutrition). (see table below).

Components of Child-Turcotte's scoring	Total score and Child's class
<ul style="list-style-type: none">• Ascites• Serum bilirubin• Serum albumin• Hepatic Encephalopathy• Prothrombin time	<ul style="list-style-type: none">• Class A = 5-6• Class B = 7-9• Class C = 10-15

- Recently the Child-Pugh system has been replaced by the **Model for End-stage Liver Disease (MELD)** score for assessing the need for liver transplantation.
- **MELD scoring** includes:
 - INR
 - Serum bilirubin
 - Serum creatinine
- A MELD score of > 14 is required for liver transplantation listing.
- A similar system, **PELD** (pediatric end-stage liver disease), is based on INR, serum bilirubin, serum albumin, age, and nutritional status and is used for children <12 years of age.

LIVER TRANSPLANTATION

- Liver transplantation was pioneered in the 1960s by **Starzl** at the University of Colorado.
- **Prognosis in cirrhosis** can be assessed by **Child-Pugh score** and **MELD (Model for End-stage Liver Disease) score** (see at start of this chapter).
- Currently, cirrhosis due to **chronic hepatitis C and alcoholic liver disease** are the MC indications for liver transplantation, accounting for over 40% of all adult candidates who undergo the procedure:
 - MC indication in adults = end stage cirrhosis
 - MC indication in children = biliary atresia.

Criteria for Orthoptic Liver Transplantation in Acute Liver Failure

- Paracetamol induced pH <7.30 (irrespective of grade of encephalopathy) or prothrombin time (PT) >100 s + serum creatinine >300 µmol/L + grade 3 or 4 encephalopathy.
- Nonparacetamol induced (irrespective of encephalopathy) PT >100 s
- Or any three of the following:
 - Age <10 years or >40 years
 - Aetiology non-A, non-B, halothane or
 - Idiosyncratic drug reaction
 - More than 7 days' jaundice before encephalopathy
 - PT >50 s
 - Billrubin >300 µmol/L.

Hepatectomy Terminology

- **Right hepatectomy:** Removes four segments 5,6,7,8.
- **Left hepatectomy:** Removes three segments 2, 3, 4.
- **Trisegmentectomy:** Removal of any combination of three segments
- **Extended right hepatectomy:** Involves five segments; a right hepatectomy, which extends into segments 1 or 4
- **Extended left hepatectomy:** Involves four segments; a left hepatectomy, which extends into segments 1, 5 or 8.

GALLBLADDER

PATHOLOGY OF BILIARY TREE

1. Caroli's disease:

- Congenital, segmental dilatation of intrahepatic biliary tree; complicated by cholelithiasis, hepatic abscesses, cholangiocarcinoma.

- When a/w congenital hepatic fibrosis it is called Caroli's syndrome.
- "**Central dot sign**" seen on CT scan and also on Ultrasound.
- 2. **Klatskin tumors:** Are tumors arising at the confluence of right and left hepatic bile ducts, notable for slow

growth, sclerosing behavior and infrequency of distant metastasis.

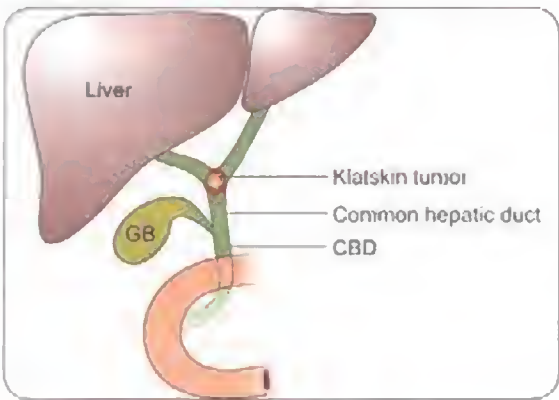


Fig. 22.16: Klatskin tumor

BILARY CIRRHOSIS

Primary biliary cirrhosis

- Intrahepatic, autoimmune disorder; MC in females
- MC symptom: **pruritus**; severe obstructive jaundice, steatorrhea, hypercholesterolemia (xanthomas)
- ↑ALP, ↑**Antimitochondrial Ab**
- Periportal fibrosis
- A/w **scleroderma, CREST**

Secondary biliary cirrhosis

- Extrahepatic biliary obstruction
- In pressure in intrahepatic ducts → Injury/fibrosis.
- Often complicated by ascending **cholangitis**, bile stasis and 'bile lakes'
- ↑ALP, ↑**conjugated bilirubin**

Primary sclerosing cholangitis

- Both intra- and extra-hepatic obstruction.
- Inflammation and fibrosis of bile ducts → alternating strictures and dilation with "**beading**" on ERCP.
- Concentric '**onion skin**' bile duct fibrosis.

Contd...

Contd..

- Fatigue, intermittent jaundice, weight loss, RUQ abdominal pain and pruritus
- ↑ALP, ANA, p-ANCA, anti-Sm antibodies
- A/w **ulcerative colitis, HIV**

GALLSTONES

- Gallstones form when solubilising bile acids and lecithin are overwhelmed by ↑ cholesterol and/or bilirubin.
- **Risk factors** for gallstones: "**4 Fs**: Fat, Female, Fertile, Forty".
- 2 types of stones:
 - **Cholesterol stones:**
 - **Radiolucent**; MC type of gallstones.
 - A/w obesity, Crohn's disease, cystic fibrosis, advanced age, clofibrate, estrogens, multiparity, rapid weight loss.
 - **Pigment stones (radioopaque):**
 - **Black pigment stones** common in India; Seen in patients with chronic RBC hemolysis, alcoholic cirrhosis, advanced age, cystic fibrosis; prosthetic valve; contain mainly **calcium bilirubinate**; arise in sterile gallbladder bile.
 - **Brown pigments stones** form in the bile duct and are a/w bile stasis and infections in biliary tree.
- **Complications of gallstones:**
 - Acute calculous cholecystitis.
 - Ascending cholangitis: RUQ pain, fever, jaundice (**Charcot's triad**)
 - CBD stones
 - **Rigler's triad:** Air in biliary tree (pneumobilia), small bowel obstruction and ectopic gallstone.
 - Ca gallbladder
 - Gallstone ileus or **Bouveret's syndrome**.

DISEASES OF THE BILIARY TRACT

	Clinical Features	Diagnosis	Treatment
Gallstones	Asymptomatic	U/S	None
Symptomatic Gallstones	Biliary pain	U/S	Laparoscopic cholecystectomy
Cholesterosis of gallbladder	Usually asymptomatic	Oral cholecystography	None
Adenomyomatosis	May cause biliary pain	Oral cholecystography; comet tail artefact on U/S	Laparoscopic cholecystectomy if symptomatic

Contd

Contd...

	Clinical Features	Diagnosis	Treatment
Porcelain gallbladder	Usually asymptomatic, high risk of gallbladder Ca (20–30%)	X-ray or CT	Laparoscopic cholecystectomy
Acute cholecystitis	Epigastric or right upper quadrant pain, nausea, vomiting, fever, Murphy's sign (inspiratory arrest during deep palpation of RUQ)	Leukocytosis, U/S, HIDA scan	Antibiotics, laparoscopic cholecystectomy
Chronic cholecystitis	Biliary pain, constant epigastric or right upper quadrant pain, nausea	U/S (stones), oral cholecystography (nonfunctioning gallbladder)	Laparoscopic cholecystectomy
Cholelithiasis (stone in bile duct)	Asymptomatic or Charcot's triad (biliary colic, jaundice, fever); gallstone pancreatitis	Leukocytosis and positive blood cultures in cholangitis; elevated amylase and lipase in pancreatitis, U/S (dilated ducts), endoscopic retrograde cholangiopancreatography (ERCP) is gold standard investigation	Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis
Diverticulosis of GB	Usually manifest as black pigment stones impacted in lacunae of Luschka	Oral cholecystography	Laparoscopic cholecystectomy
Choledochal cyst	Congenital fusiform dilatation of common bile duct. F:M=4:1; Commoner in Japanese ; 60% present before 10 years of age; 1/3 show classic triad of upper abdominal pain, jaundice and upper abdominal mass; treat by hepaticojejunostomy; risk of cholangio-Ca in older age presentation	U/S, Oral cholecystography	Cyst may contain 1–2 litres. Excision of cyst and cholecho-jejunostomy since Ca may develop in cyst
Torsion of GB	May occur where GB has a long mesentery ' Floating GB '. Sudden agonizing pain with vomiting and shock. If GB becomes gangrenous/ ruptures pain stops instantly.		Laparoscopic cholecystectomy

Key: ERCP = Endoscopic retrograde cholangiopancreatography; HIDA = Iminodiacetic acid; GB = Gallbladder; LC = Laparoscopic cholecystectomy; OC = Oral cholecystography; RUQ = Right Upper Quadrant; US = Ultrasound.

Ultrasound Features of Acute Cholecystitis

- Presence of **gallstones** in gallbladder-highly reflective echogenic focus within gallbladder lumen, normally with prominent posterior acoustic shadowing.
- **Sonographic Murphy sign:** Tenderness over gallbladder with ultrasound transducer
- Gallbladder **mural wall thickening (> 3 mm)**
- **Echo-poor halo** in or around the GB wall or striated GB wall (indicative of edema)
- **Periocholecystic fluid**
- Gallbladder **distension** (about 93% of patients with GB volume >70 mL have acute cholecystitis).

PANCREAS

ACUTE PANCREATITIS

Etiology

- **Gallstones** (MC cause), **Ethanol** (2nd MC), **Trauma**, **Steroids**, **Mumps**, **Autoimmune** (PAN), **Scorpion venom**, **Hyperlipidemia** (raised Ca²⁺, hypothermia), **ERCP** (also emboli), **Drugs** (asparaginase, azathioprine, didanosine, diuretics, mercaptopurine, OCPs, pentamidine, tetracycline, Valproic acid), also pregnancy. ("**GET SMASHED**")
- **Autodigestion** is a pathogenic theory of **acute pancreatitis** according to which pancreatitis results when **proteolytic enzymes** (e.g. **trypsinogen, chymotrypsinogen, proelastase and phospholipase A**) are activated in the pancreas **rather than** in the intestinal lumen.

- **Clinically:**
 - Midepigastric tenderness, that *radiates to the back, may be relieved by sitting/leaning forward* and lasts for hours to days,
 - - ↓ bowel sounds, jaundice and fever.
 - **Cullen's sign** (periumbilical ecchymoses) and **Grey Turner' sign** (flank ecchymoses) reflect **retroperitoneal hemorrhage**
- **Tests:**
 - **Serum lipase** (*greatest specificity*) and **serum amylase** are ↑, ↑ ALT
 - CXR: pleural effusion; AXR: '**sentinel**' loop, '**colon cut off**' sign, **renal halo** sign, pancreatic calcification
 - **CT scan:** fuzzy outline of Pancreas; peripancreatic fluid collection, enlarged pancreas, necrosis, blurring of fat planes.
- **Treatment:**
 - Supportive (NPO, IV fluids, pain management)
 - ERCP with papillotomy; cholecystectomy.
 - **Complications:** Pseudocyst, necrosis, abscess.
 - **Metabolic complications** include **hypocalcemia** (*poor prognosis*), **hyperlipemia**, **hyperglycemia**, and **diabetic ketoacidosis**.
- **Pseudocyst:**
 - A pseudocyst is a collection of amylase-rich fluid enclosed in a wall of fibrous or granulation tissue.
 - Formation of a pseudocyst requires 4 weeks or more from the onset of acute pancreatitis.
 - Fluid from a pseudocyst typically has a low CEA level, and levels above 400 ng/mL are suggestive of a mucinous neoplasm.
 - Pseudocysts will resolve spontaneously in most instances.

Ranson Imrie Scoring

- For **predicting severity of acute pancreatitis** – Valid for alcohol induced pancreatitis only.

At admission	In the first 48 hours
Serum LDH > 350 units/L	Serum Calcium < 8 mg/dL (2 mmol/L)
Age > 55 years	Hematocrit drops by more than 10%
Blood Glucose > 200 mg/dL	Arterial PO ₂ < 60 mmHg
AST > 250 units/L	Base deficit > 4 mEq/L
WBC counts >16,000/mL	BUN rise > 5mg/dL
" LAGAW "	Fluid Sequestration of > 6 litres
	" Calvin and HOBBeS "

Glasgow Score

At admission	In the first 48 hours
• Age > 55 years	• Serum calcium < 2 mmol/L
• WBC count > i5 X 10 ⁹ /L	• Serum albumin < 32 g/L
• Blood glucose > 10 mmol/L	• LDH > 600 units/L
• Serum urea > 16 m mol/L (no response to IV fluids)	• AST/ALT > 600 units/L
• Arterial oxygen saturation, PaO ₂ < 8 kPa (60 mm Hg)	

EXTRA EDGE

- Both in the **Ranson Imrie** and **Glasgow** scores, disease is classified as **severe when 3 or more factors** are present
- **Balthazar** and **Mortele** scores are used for grading severity of pancreatitis on CT scan.

Balthazar Score

- Balthazar score is used in CT severity index (CTSI) for grading of acute pancreatitis; The maximum score that can be obtained is 10.

Grading of pancreatitis	Pancreatic necrosis
• A = normal pancreas - 0	• none - 0
• B = enlargement of pancreas - 1	• less than/equal to 30% - 2
• C = inflammatory changes in pancreas and peripancreatic fat - 2	• 30-50 % - 4
• D = ill defined single fluid collection - 3	• 50% - 6
• E = two or more poorly defined fluid collections - 4	

- **Mild pancreatitis** (interstitial pancreatitis): **Balthazar B or C**, without pancreatic or extrapancreatic necrosis
- **Intermediate** (exudative pancreatitis): **Balthazar D or E**, without pancreatic necrosis; peripancreatic collections are due to extrapancreatic necrosis.

- **Severe pancreatitis** (necrotizing): with pancreatic necrosis.

CHRONIC PANCREATITIS

Causes of Chronic Pancreatitis

- MC Cause: **High alcohol consumption** (60–70% cases)
- **Obstructive: Stenosis of ampulla of Vater**
- Pancreas divisum, annular pancreas
- Cystic fibrosis
- Hereditary (chromosome 7)
- Idiopathic (30% cases)

EXTRA EDGE

- BUT only 5–10% of people with alcoholism develop chronic pancreatitis.
- In both **acute** and **chronic pancreatitis**, **pain is the cardinal symptom**.

Ultrasound Features of Chronic Pancreatitis

- (≥ 4 features highly suggestive):
- Presence of stones
 - Visible side branches, cysts, lobularity
 - Irregular main pancreatic duct
 - Hyperechoic foci and strands
 - Dilated main pancreatic duct
 - Hyperechoic margins of the main pancreatic duct

MORE PANCREAS HIGH YIELD

- Harmless acute pancreatitis score = **HAPS**
- Bedside Index for Severity in Acute Pancreatitis = **BISAP**
- **Pancreatitis in children**: MC cause is **blunt abdominal trauma**

- **Pancreatitis in AIDS**: (1) Pancreatic infection with CMV, cryptosporidium and MAC an (2) drugs such as didanosine, pentamidine, trimethoprim-sulfamethoxazole, and protease inhibitors.
- **Pancreatitis, recurrent**: occurs in **25% cases**.
- **“Gold standard”** enzyme for acute pancreatitis: **serum lipase** (3 fold elevation)
- **For chronic pancreatitis**: The diagnostic test with the **best sensitivity and specificity** is the hormone stimulation test utilizing **secretin**.
- In **Southern India**, **chronic calcific pancreatitis** occurs in **non-alcoholics**, possibly as a result of **malnutrition and cassava consumption**.

MORE HIGH YIELD POINTS

- **Peliosis hepatis** may be caused by anabolic steroids and oral contraceptive steroids as well as azathioprine and mercaptopurine, which may also cause nodular regenerative hyperplasia.
- Liver biopsy may show characteristic periductal fibrosis (“onion-skinning”) in primary biliary cirrhosis.
- Inv. Of choice for Ca pancreas: **Contrast Enhanced CT**.
- MC surgery for Ca pancreas: **Whipple’s operation**.
- MC complication of Whipple’s operation: **Disruption of gastric anastomosis**.
- **Metastases to liver** shows multiple **umbilicated nodules**.

Note

- Viral hepatitis - microbiology, pathology and treatment has been discussed under microbiology chapter (Pg 271).


RENAL SYSTEM

CONGENITAL ANOMALIES OF THE KIDNEY

Condition	Remarks
Renal aplasia	
Absence of one kidney	Discovered Incidentally on ultrasound, IVU or CT scan. Contralateral kidney is hypertrophied
Renal ectopia	
Pelvic kidney	The kidney does not ascend, but remains near the pelvic brim, usually left sided . Contralateral kidney is in normal position.
Horseshoe kidney	Usually lower poles are fused with junction in front of L4 vertebra . Ureters pass in front of the fused lower poles. On IVU, lower pole calyces on both sides are directed towards the midline and ureters have flower-vase-like curves. MC in men.

Contd...

Contd...

Condition	Remarks
	
Fig. 22.17: Horseshoe kidney showing fusion of the lower poles	
Crossed dystopia	Unilateral fusion. Both kidneys are in one loin and usually fused. Maybe unilateral long kidney or unilateral S-shaped kidney . Ureter of the lower kidney crosses midline to enter bladder on the contralateral side.
Aberrant renal vessels	
Multiple renal arteries	Two or more renal arteries occur MC in women and unilaterally on the left and veins. Renal arteries, being, end-arteries, should be preserved, but renal veins have extensive collaterals and an aberrant renal vein can be divided .
Duplication	
Duplex renal pelvis	MC abnormality of upper renal tract. Usually unilateral and more common on left. “Drooping Lily” sign seen on IVU in Duplex renal collecting system.
Duplex ureter	Ureters often join before they reach the bladder and open by a common ureteric orifice, they may also open independently. In females , ectopic ureter opens either into the urethra below the sphincter or into the vagina causing incontinence . In males , the aberrant opening is above the external urethral sphincter so that the patient is continent. Weight-Mayer rule : Upper pole ureter inserts medially and inferior (caudal) to lower pole ureter.
Postcaval ureter	The right ureter passes behind the inferior vena cava instead of lying to the right.
Ureterocele	More common in women. Cystic enlargement of intramural portion of ureter thought to result from congenital atresia of ureteric orifice. IVU shows “adder head” or “cobra head” appearance.

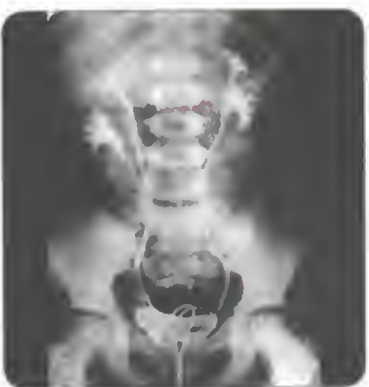


Fig. 22.18: X-ray showing bilateral duplex system

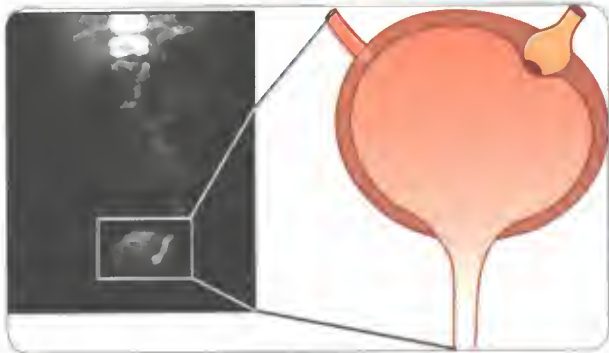
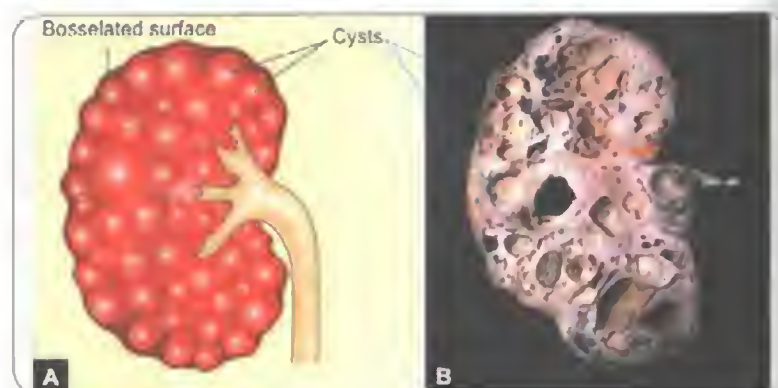


Fig. 22.19: IVU reveals left sided ureterocele with duplex kidney. Note the characteristic Cobra (Adder) head pattern of left ureterocele



Fig. 22.20: IVU showing flower vase appearance of horseshoe kidney



Figs. 22.21A and B: Autosomal-dominant adult polycystic kidney disease (ADPKD) shows markedly enlarged kidney with numerous dilated cysts. A. External surface (Diagrammatic); B. Cut section

Autosomal Recessive (Childhood) Polycystic Kidney	Autosomal Dominant (Adult) polycystic kidney
Genetics <ul style="list-style-type: none"> ARPKD gene— chromosome 6p. Gene defect – PKHD1 which produces fibrocystin (polyductin). (PKHD1 = Polycystic Kidney Hepatic Disease 1). 	<ul style="list-style-type: none"> APKD-1 gene on chromosome 16p. ("Polycystic kidney" = 16 letters = 16p!) Gene defect – PKD1 and PKD2 which code for polycystin 1 and 2. Phenotypic heterogeneity is a hallmark of ADPKD, as evidenced by family members who share the same mutation but have a different clinical course.
Clinically <ul style="list-style-type: none"> Diagnosed in first year of life presenting as bilateral abdominal masses. Enlarged, with small cysts, <5 mm, limited to the collecting tubules. Death in neonatal period is MC due to pulmonary hypoplasia. HTN occurs in first few years of life. Longer-term survivors frequently develop portal hypertension, esophageal varices, and hypersplenism from peripartal fibrosis. 	<ul style="list-style-type: none"> DOES NOT manifest before 30 years. Manifests disease as renomegaly, flank pain, hematuria, infection, hypertension, uremia.
Associated abnormalities <ul style="list-style-type: none"> Congenital hepatic fibrosis. Maternal oligohydramnios Potter's syndrome. 	<ul style="list-style-type: none"> Hepatic cysts (MC extrarenal anomaly). Also cysts in spleen, pancreas, ovaries). Intracranial Berry aneurysms. mitral valve prolapse, Colonic diverticula.
Imaging <ul style="list-style-type: none"> U/s shows large, echogenic kidneys The diagnosis can be made in utero after 24 weeks of gestation in severe cases, but cysts generally become visible ONLY AFTER birth. The absence of renal cysts in either parent on ultrasonography helps to distinguish ARPKD from ADPKD in older patients. 	<ul style="list-style-type: none"> IVU — "spider-leg" deformity. The sensitivity of renal ultrasonography for the detection of ADPKD is 100% for subjects 30 years or older with a positive family history. Before the age of 30 years, CT scan or T2-weighted MRI is more sensitive for detecting presymptomatic disease.
Treatment	<ul style="list-style-type: none"> Ravling operation.

RENAL STONES

- Etiology**
 - Hyperparathyroidism
 - Decreased urinary citrate
 - Deficiency of vitamin A
 - Dehydration (high fluid intake is the best prophylactic measure)
 - Urinary stasis; prolonged immobilization.
- Clinical Features:**
 - Pain in the renal angle
 - Ureteric colic:
 - Agonising pain passing from the loin to the groin.
 - Radiates to the groin, penis, scrotum or labium as the stone
 - Progresses down the ureter
 - Severity of pain is not related to stone size
 - Hematuria is very common.
- Gold standard test is **helical CT without contrast**.
- X-ray 'KUB' film shows the kidney, ureters and bladder.
 - An opacity maintaining its position relative to the urinary tract during respiration is likely to be a calculus.

Opacities on a plain abdominal radiograph that may be confused with renal calculus

- Calcified mesenteric lymph node
- Gallstones or concretion in the appendix
- Tablets or foreign bodies in the alimentary canal (e.g. cyclopenthiizide)
- Phleboliths – calcification in the walls of veins, especially in the pelvis
- Ossified tip of the 12th rib
- Calcified tuberculous lesion in the kidney
- Calcified adrenal gland.

- Conservative management:**
 - Calculi smaller than 0.5 cm pass spontaneously unless they are impacted. Surgical intervention should be avoided.
- Surgical:**
 - Infection in an upper urinary tract obstructed by stone is dangerous and needs urgent surgical intervention.
- Surgery for renal stones:**
 - Minimal access surgery: Percutaneous nephrolithotomy; ESWL – Extracorporeal Shockwave Lithotripsy
 - Open surgery: Pyelolithotomy; nephrolithotomy.
- Surgery for ureteric stones:**
 - Endoscopic stone removal with Dormia basket
 - Open surgery: Ureterolithotomy.

Type	Etiology	Comments
Calcium stones (MC – 80%) Calcium oxalate (MC) Calcium phosphate	Hypercalciuria secondary to – hypercalcemia, primary hyperparathyroidism, distal RTA, bowel surgery (hyperoxaluria), indinavir therapy	Radiopaque <i>Hard and irregular with sharp projections</i> MC in men , familial predisposition;
Mixed (Struvite) stones Triple phosphate – magnesium-ammonium-calcium phosphate	UTI with <i>Proteus</i> (has urease) Staghorn calculus – fills renal pelvis and calyces	Radiopaque, <i>Smooth and dirty white</i> MC in women , struvite crystals resemble coffin lids
Uric acid stones	Hyperuricemia – Gout, Lesch Nyhan syndrome, myeloproliferative disorders, malignant tumors	Radiolucent; (" URIC = U Radiologically I nvisible C alculus!") Multiple and multifaceted stones
Cystine stones (least common)	Cystinuria	Radiopaque due to sulphur content; yellow crystalline sparkling stones; VERY Hard – relatively resistant to lithotripsy



Fig. 22.22: A plain X-ray, KUB, revealing staghorn calculus on right side



Fig. 22.23: Staghorn calculus

EXTRA EDGE

- **Ammonium urate** stones are seen in **laxative abuse**.

Predisposing Factors for Iatrogenic Urologic Injury

- Uterus size larger than 12 weeks' gestation
- Large ovarian cysts 4 cm or larger
- **Endometriosis**
- **Pelvic inflammatory disease**
- Prior intra-abdominal operation
- Radiation therapy
- **Broad ligament fibroid**
- Advanced state of malignancy
- Anatomical anomalies of the urinary tract (ectopic ureter, duplex ureter, etc.).

BLADDER CONDITIONS

Bladder Rupture

- **Extraperitoneal** rupture (**MC, 80%**): caused by blunt trauma or **surgical damage**.
- **Intraperitoneal (20%)**: usually secondary to a blow or fall on a distended bladder.
- **Retrograde cystography** will confirm the diagnosis.
- Treatment:
 - **Extravesical injury**—catheter drainage for 10 days
 - **Intraperitoneal injury**—laparotomy, repair and bladder drainage.

Normal cystometry findings/values

- Residual urine < 50 mL
- First desire to void occurs between 150–250 mL
- Strong desire to void does not occur until after 250 mL
- Cystometric capacity between 400–600 mL
- No uninhibited detrusor contractions during filling, despite provocation

Contd...

Contd...

Normal cystometry findings/values

- No urge or stress incontinence despite provocation
- Voiding occurs as a result of voluntarily initiated and sustained detrusor contraction
- Flow rate during voiding is greater than 15 mL/sec with a detrusor pressure of < 50 c H₂O.

Urinary Fistulae

- A fistula is a communication between two epithelium lined surfaces.
- **Vesicovaginal fistula** is **MC** and result from **obstetric trauma**; an associated ureterovaginal fistulae occurs in about 10 percent of cases.
- A '**three-swab test**' is used to aid the diagnosis.
- Main management is surgical.
- The principles of repair include *good exposure, excision of diseased tissue and tension-free vascularized repair* in anatomic layers.
- Fistulae caused by **radiation, cancer** and **sepsis** can be complex with **multiple tracts**.
- The persistence of a fistula on the skin implies the presence of distal obstruction, chronic infection, such as tuberculosis, or a foreign body, such as a stone or nonabsorbable ligature.

How to remove a retained/stuck Foley's catheter?

- The **BEST** way - is to further inflate the balloon with 20 mL of water and then burst the balloon percutaneously using a needle under ultrasound screening.
- After, the balloon bursts, it is important to subsequently cystoscope the patient to ensure that any fragments are removed before they can form a foreign body calculus. (ALSO KNOW: MC foreign body in the urinary bladder is fragment of a catheter balloon!)
- Cutting off the side arm and attempting to clear the channel with a wire is only occasionally successful.

THYROID

Benign and Malignant Thyroid Nodules on U/S

Features	Benign	Malignant
Echogenicity	Hyperechoic	Markedly Hypoechoic or heterogeneous
Margins	Smooth border or complete/thin halo	Irregular border or invasion into adjacent tissue – irregular halo
Colloid microcrystals	Comet tail sign	—
Calcifications	Peripheral (eggshell)	Microcalcifications
Vascularity	Peripheral	Irregular intranodular/ central vascularity
Shape	Flattened	Rounded
Lymph-adenopathy	Absent	Present
Cyst	Thin walled	Thick walled

EXTRA EDGE

- Only **macroscopic capsular breach** and **nodal involvement** are **diagnostic of malignancy** (Bailey and Love, 26th).

Radioactive Iodine

- **I¹³¹** is used for radioactive iodine **therapy** (**beta rays** are used)
- **I¹²³** is used for **diagnostic studies** (**Gamma rays** are used)
- High dose of **retinoic acid** will make **I¹³¹** to **concentrate in tumor cells**.

Thyroid Enlargement

- The normal thyroid gland is **impalpable**.
- The term **goiter** (from the Latin *guttur* = *the throat*) is used to describe generalized **enlargement** of the thyroid gland.
- Goitrogens are the vegetables of the brassica family (cabbage, kale and rape), which contain thiocyanate, drugs such as para-aminosalicylic acid (PAS) and, of course, the antithyroid drugs (**Thiocyanates** and **perchlorates** interfere with iodide trapping; **carbimazole** and **thiouracil** compounds interfere with the oxidation of iodide and the binding of iodine to tyrosine).
- The most important factor in **endemic goiter** is **dietary deficiency of iodine**.
- The **daily requirement of iodine** is about **0.1–0.15 mg**.
- **Diffuse hyperplastic goiter** corresponds to the **first stages** of the **natural history of goiter**.
- A **colloid goiter** is a late stage of diffuse hyperplasia when TSH stimulation has fallen off and when many follicles are inactive and full of colloid.

- An increased incidence of **cancer** (**usually follicular**) has been reported from endemic areas.

Thyroid Operations

- All thyroid operations can be assembled from three basic elements:
 - Total lobectomy
 - Isthmusectomy
 - Subtotal lobectomy
- Total thyroidectomy = 2 × total lobectomy + isthmusectomy
- Subtotal thyroidectomy = 2 subtotal lobectomy + isthmusectomy
- Near-total thyroidectomy = total lobectomy + isthmusectomy + subtotal lobectomy (**Dunhill** procedure)
- Lobectomy = total lobectomy + isthmusectomy

Retrosternal Goiter

- This is often symptomless and discovered on a routine chest radiograph
- Most arise from the lower pole of a nodular goiter
- Dyspnea, particularly at night, cough and stridor (harsh sound on inspiration)
- Dysphagia
- Engorgement of facial, neck and superficial chest wall veins; in severe cases there may be obstruction of the superior vena cava).
- Recurrent nerve paralysis is rare
- Treatment is by surgical resection.

More MCQ Points

- **Kocher** (Switzerland) is called "**father of thyroid surgery**". He is **first surgeon to get Nobel prize**.
- Other surgeons who got Nobel prize are:
 - **Alexis Carrell** for **vascular anastomosis**
 - **Christiaan Barnard** for **heart transplantation**
 - **Charles Huggins**, urologist, for **management of Ca prostate**.

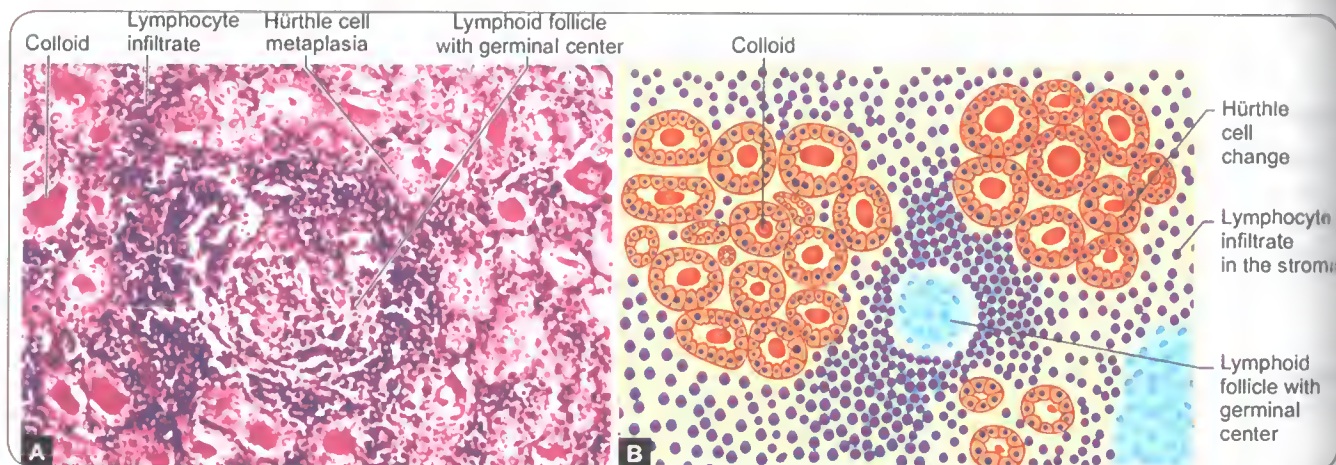
Thyroid Cancers

- The vast majority of primary malignancies are carcinomas derived from the **follicular cells**.
- Follicular epithelium—**differentiated** (Follicular, papillary).
- Follicular epithelium—**undifferentiated** (Anaplastic).
- **Dunhill** classified them histologically as **differentiated and undifferentiated**; and the differentiated carcinomas are subdivided into follicular and papillary.
- Most important etiological factor in thyroid malignancy (esp. papillary) is **thyroid irradiation** under 5 years of age (see Table).

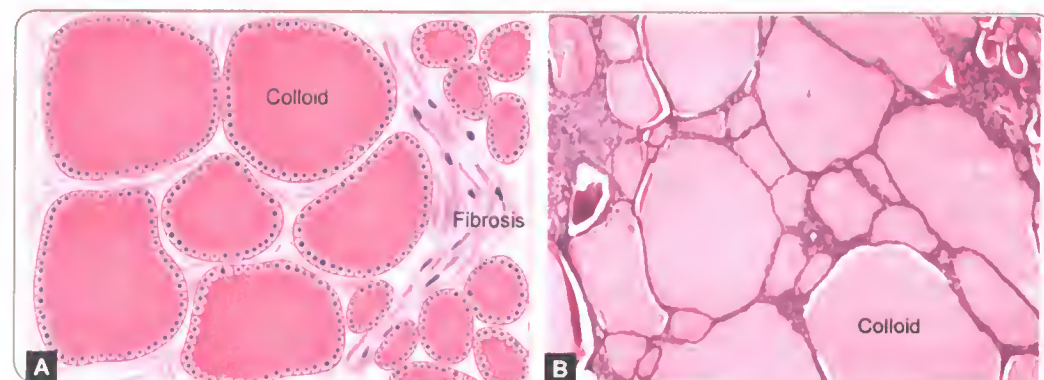
Type	Cells Affected	Characteristics	Prognosis
Papillary	Columnar cells of gland	MC thyroid Ca (80% cases); more common in younger patients Begins as slow-growing nodule; lymphatic metastasizes to local cervical lymph nodes ; Orphan Annie (ground glass) nuclei; Psammoma bodies ; ↑ risk with childhood irradiation . ("Remember As Papillary – to LYmph nodes")	Excellent ; few recurrences
Follicular	Cuboid cells in follicles	MC in older patients; May function like normal thyroid tissue; hematogenous metastasizes to liver, lung, bone, and brain	Good but worse than papillary cancer; 50% 10-year survival
Medullary	Parafollicular C cells	Produces calcitonin ; may present with other endocrine tumors (e.g., MEN2a and MEN2b , a/w ret oncogene)	Worse in older patients; metastases common at diagnosis
Anaplastic	Poorly differentiated	Very aggressive ; local extension causes hoarseness, dysphagia	Very Poor

EXTRA EDGE

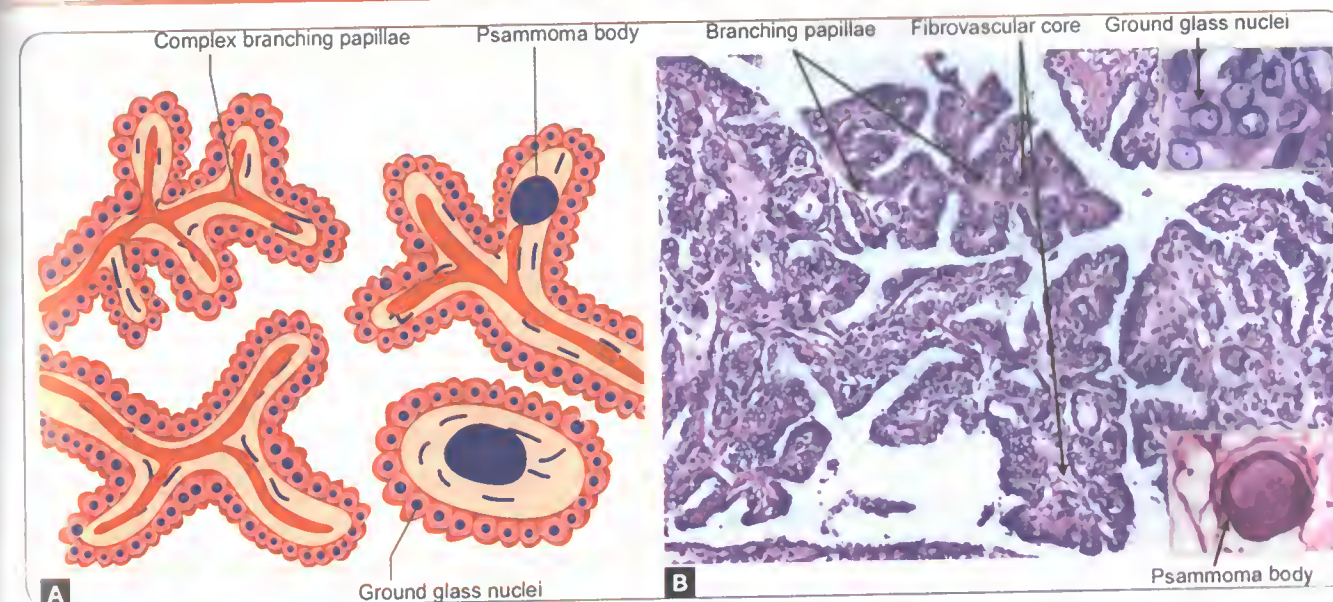
- Follicular adenoma: benign tumor; can be differentiated from follicular ca only by **histology**; in adenoma there is NO invasion of capsule or blood vessels; Treatment is by **lobectomy**
- Hurthle cell tumors** are a variant of follicular neoplasm in which oxyphil (*Hurthle, Askanazy*) cells predominate histologically. Hurthle cell cancers are associated with a poorer prognosis.



Figs. 22.24A and B: (A) Photomicrograph; (B) Diagrammatic. Microscopy of Hashimoto thyroiditis shows parenchyma densely infiltrated by lymphocytes with germinal centers. Some of the thyroid follicles lined by deeply eosinophilic Hurthle cells



Figs. 22.25A and B: A. Photomicrograph; and B. Diagrammatic. Microscopy of a multinodular goiter composed of thyroid follicles of varying sizes distended with variable amount of colloid.



Figs. 22.26A and B: A. Photomicrograph; B. Diagrammatic. Papillary carcinoma of the thyroid shows well-formed, branching papillae lined by cells with characteristic empty-appearing ("Orphan Annie eye") nuclei. Inset in A: upper right shows Orphan Annie eye nuclei and nuclear groove and right lower shows psammoma body.

EXTRA EDGE

Oncogenes associated with thyroid cancers are:

- Papillary thyroid Ca: RET, BRAF, NTRK-1; RAS
- Follicular thyroid Ca: RAS, PAX-8-PPAR gamma
- Medullary thyroid Ca- RET

BREAST**NIPPLE CONDITIONS****Nipple Discharge**

Colour of discharge	Cause
Blood-stained	Duct papilloma (MC) Intraductal carcinoma Duct Ectasia
Serous	Fibrocystic disease Duct Ectasia Carcinoma
Green or black	Duct Ectasia

Treatment of Nipple Discharge

- Excision of affected ducts: Microdochectomy
- Subareolar resection - cone excision of major ducts (Hadfield's procedure).

Other Nipple Conditions

- Cracked Nipple:** may occur during lactation and be the forerunner of acute infective **mastitis**.
- Papilloma of the nipple** should be excised with a tiny disc of skin OR the base may be tied with a ligature and the papilloma will spontaneously fall off.
- Retention cyst** of a gland of Montgomery: These glands are situated in the areola and secrete sebum; if they become blocked a sebaceous cyst forms.
- Eczema of the nipples** is a rare condition and is often **bilateral**; usually a/w **eczema elsewhere on the body** (look in **cubital fossae**). It is treated with 0.5 per cent hydrocortisone.
- Paget's disease of the nipple** is caused by malignant cells in the subdermal layer and is usually a/w a carcinoma within the breast; must be distinguished from eczema.

CONGENITAL BREAST ANOMALIES

- **Athelia** = Absence of the nipple, areola
- **Polythelia** = supernumerary nipple and areola
- **Amastia** = complete absence of breast development
- **Polymastia** = accessory breast; MC in axilla
- **Amazia** = nipple is present BUT glandular tissue absent
- **Poland's syn:** Congenital absence of the breast (amazia) associated with absence of *sternal portion of pectoralis major*.

Mondor's disease

- **Mondor's disease** is **thrombophlebitis of the superficial veins of the breast** and anterior chest wall, although it has also been encountered in the arm.
- Cause is obscure. **Pathognomonic feature** is **thrombosed subcutaneous cord**, usually attached to the skin.
- The only **treatment required** is **restricted movements of the arm** and in any case the **condition subsides within a few months** without recurrence, complications or deformity.

ACUTE MASTITIS

- Breast abscess, *during breast feeding*
- Risk of bacterial infection through cracks in the nipple
- MC due to *S. aureus*
- **Feeding may continue** on affected side if patient can manage
- Treat with **co-amoxiclav**
- For non resolving abscess - **repeated aspiration under antibiotic cover** with U/S guidance;
- If still not resolved **I and D** necessary.



Fig. 22.27: Typical breast abscess with features of acute inflammation. Drain should be placed after incision and drainage in such abscesses. Often gauze drain can be used

DUCT ECTASIA (PERIDUCTAL MASTITIS)

- This is a **dilatation of the breast ducts**, which is often a/w periductal inflammation.
- Much more common in **smokers**.
- **Nipple discharge** (of any colour), a **subareolar mass**, **abscess**, **mammary duct fistula** and/or **nipple retraction** are the MC symptoms.
- In the case of a mass or nipple retraction, a carcinoma must be excluded by obtaining a mammogram and negative cytology or histology. If any suspicion remains the mass should be excised.
- **Surgery** is often the **only option** likely to bring about cure of this **notoriously difficult condition**; this consists of excision of all of the major ducts (**Hadfield's operation**).

More Breast Lesions

- **ANDI:** The nomenclature of benign breast disease is confusing. To address this confusion, a concept (aberrations of normal development and involution (ANDI)) has been developed and described by the Cardiff Breast Clinic.
- **Traumatic Fat necrosis:** A benign painless lump due to injury to breast tissue.
- **Gynecomastia:** Results from hyperestrogenism (clrhosis, testicular tumor, puberty, old age), Klinefelter' syndrome or drugs (digitalis, isoniazid, spironolactone, cimetidine, ketoconazole, oestrogen, heroin, alcohol, marijuana) ("**DISCKOS HAM!!**").
- **Zuska's disease:** recurrent periductal mastitis



Fig. 22.28: Right-sided gynecomastia (well-localised—puffy nipple)

BENIGN BREAST TUMOURS

Fibroadenoma

- **MC benign tumour**, < 25 years
- Small **mobile firm mass** with **sharp edges**.
- Size and **tenderness with pregnancy**.
- **NOT** a precursor to breast cancer.
- **Giant fibroadenoma** (>5 cm) occurs in the Afro-Caribbean population and can be enucleated by submammary incision.

FNAC findings of fibroadenoma include

- Tightly cohesive branching antler-horn or finger-like projections of epithelial cells
- Stromal fragments (metachromatic fibrillary matrix material)
- Numerous bare bipolar nuclei, bordering and within epithelial clusters

Phyllodes Tumour

- Earlier called *Serocystic disease of Brodie* or **cystosarcoma phyllodes**.
- Common in women > 40 years
- Large bulky mass of connective tissue and cysts
- Tumour may have leaf like projections
- **it may be rarely malignant**
- Small tumors can be enucleated; larger tumors may require mastectomy.
- Small tumors may be enucleated or undergo 'wide local excision'.

BREAST CARCINOMA

Factors Associated with Increased Risk of Breast Cancer

- **Race:** White
- **Age:** Older, post-menopause (> 50 years)
- **Family history:**
 - Breast cancer in mother, sister, or daughter (especially bilateral or premenopausal)
- **Genetics** **BRCA1** or **BRCA2** mutation (Note: **male breast Ca** more often with a/w **BRCA2** than **BRCA1**)
- **Previous medical history:**
 - **Endometrial** cancer
 - Some forms of mammary dysplasia
 - Cancer in other breast
- **Menstrual history:**
 - **Early menarche** (under age 12)
 - **Late menopause** (after age 50)
- **Pregnancy:** **Nulliparous** or **late first pregnancy** (> 30 years).

Ca Breast Risk Assessment Methods

Gail Model

- **MC used** model
- Incorporates:
 - **Age** at menarche
 - **Number** of breast bopsies
 - **Age** at **first livebirth**
 - **Number** of **first degree relatives** with breast cancer.
- Predicts the cumulative risk of breast cancer according to the decade of life.

Claus Model

- Based on assumptions about the prevalence of high penetrance breast cancer susceptibility genes.
- Incorporates **more info about family history** but excludes other risk factors
- Estimates of breast cancer risk according to: decade of life based on presence of first and second degree relatives with breast cancer and their age at diagnosis.

Pathology

- Arise from mammary duct epithelium or lobular glands. Overexpression of estrogen/progesterone receptors or **erb-B2 (HER-2, an EGF receptor)** is common; affects therapy and prognosis (give tamoxifen for ER/PR-positive tumours).
- **Molecular classification** of breast cancer is based on gene expression profiling - 4 subtypes as below.

Estrogen Receptor (ER) positive tumors (60-70%)

- Luminal type A - express cytokeratons 8 and 18, have highest level of ER expression, low grade, respond best to endocrine therapy, good prognosis
- Luminal type B - more often high grade, less good prognosis

ER negative tumors (15-25%)

- HERs positive (on chromosome 17q): poor prognosis but respond to trastuzumab (herceptin)
- Basal like tumors (HER2 negative, ER and PR negative - "triple negative tumors") poorer prognosis but may respond to chemotherapy

EXTRA EDGE

- The **Oncotype Dx** breast cancer test and **Mammaprint** are genotyping test intended for **stage I or II, node negative, ER positive**.

Histologic Types

- **Noninvasive:** Ductal carcinoma in situ; early malignancy without basement membrane penetration.

- **Invasive:**
 - Invasive **ductal MC**; no specific type (76%) = firm fibrous mass, worst and most invasive.
 - **Invasive lobular** = often multiple and bilateral, orderly rows of cells
 - Medullary = fleshy, cellular lymphocytic infiltrate. Good prognosis.
 - Comedocarcinoma = ductal, caseous necrosis
 - Inflammatory = lymphatic involvement; red swollen; peu-d-orange (orange skin)
 - **Paget's disease of breast** = eczematous patches on nipple. Paget cells - large cells with clear halo in Malpighian layer of epidermis; suggest underlying carcinoma. Extramammary Paget's MC seen on *unlva*.

Breast Histologic Subtype and Risk

NO increased risk

- Adenosis (sclerosing or florid)
- Apocrine metaplasia
- Cysts (macro or micro)
- Ductal ectasia
- Fibrosis
- Fibroadenoma
- Hyperplasia (mild)
- Inflammation (mastitis, periductal mastitis, squamous metaplasia)

SLIGHTLY increased risk (1.5–2 times, baseline risk)

- Hyperplasia (moderate or florid, solid or papillary)
- Papilloma with fibrovascular core

Moderately increase risk (4–5 times baseline risk)

- Atypical hyperplasia (ductal or lobular)

Insufficient data to assign a risk

- Solitary papilloma of lactiferous sinus
- Radial Scar Lesion

Clinically

- MC location is **upper outer quadrant**.
- Most breast cancers will present as a **hard lump**, which may be a/w **indrawing of the nipple**.
- **Peau d'orange** is caused by **cutaneous lymphatic oedema** where the infiltrated skin is tethered by the sweat ducts it cannot swell, leading to an appearance like **orange skin**.
- **Cancer-en-cuirasse**: The skin of the chest is infiltrated with carcinoma and has been likened to a coat. It may be a/w a grossly swollen arm.

- **Diagnosis**: Mammography (discussed separately below), U/S, FNAC, excisional biopsy.

Triple Assessment for breast cancer

- Clinical Evaluation – Lump and regional nodes
- Imaging (ultrasound <35 years old or mammography >35 years old)
- Cytology or Histology

Prognosis of Breast Cancer

- **Axillary lymph node** involvement is the **single most important prognostic factor**.
- The **Van Nuys Index** is a classification and grading system for **DCIS** that is useful in therapeutic planning. Applying the criteria of **tumor size**, **margin width (margin clearance)** and **pathologic classification (nuclear grade)**, points are scored that predict the risk of tumor recurrence.
- Lymphatic metastases occur in the **axillary (75%)** and internal mammary nodes.
- Tumors in **posterior 1/3 of breast** are likely to spread to **internal mammary nodes**.
- **Hematogenous** spread occurs to bones - MC to **lumbar vertebrae** and is **osteolytic**.
- **Nottingham Prognostic Index (NPI)** = (0.2 X tumor size in cm) + Tumor Grade (1-3) + LN stage (1-3); used to select patients for **adjuvant treatment**.
- “**Triple-negative**” breast cancers - lack expression of HER-2; ER and PR have a **higher risk of recurrence and metastases** and **worse survival rates**.
- Prognostic factors a/w **increased recurrence in lymph node-negative** breast cancers are: Size (T2,T3), Hormone receptor **negative**; **Aneuploid** with **high histologic grade**; tumor labeling index < 3%; S-phase fraction > 5%; lymphatic /vascular invasion; **high levels** of cathepsin-D, EGFR and HER-2 oncogene.

Treatment

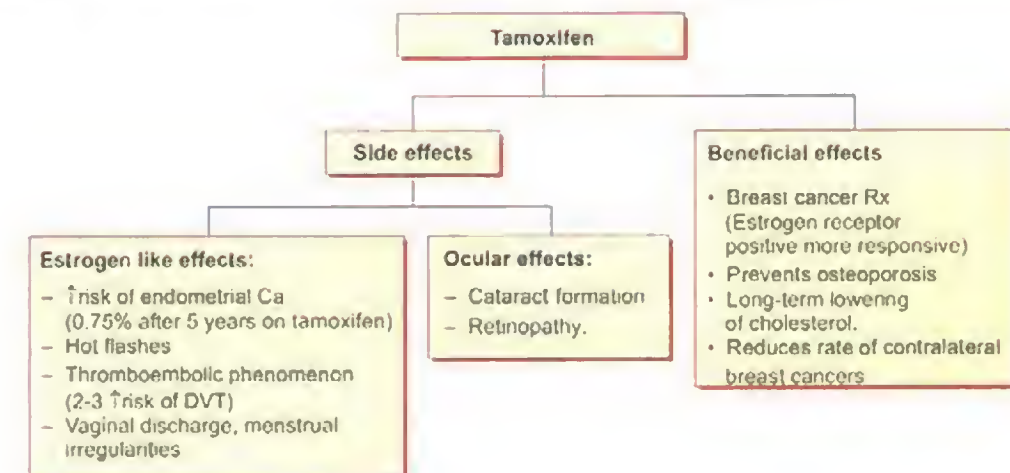
- Intraductal Ca- mastectomy or wide excision plus radiation therapy.
- For invasive breast cancer:
 - Node negative disease: **breast conservation therapy** (wide tumor excision) or modified radical mastectomy with radiation therapy.
 - **Endocrine therapy** is beneficial only for patients with ER+ or PR+ tumors.
- Surgery: see below.

Types of Endocrine Therapy for Invasive/Metastatic Ca Breast

Type of therapy	Examples	Comments
Ovarian ablation	Surgery, radiation therapy, pharmacologic interventions	
LHRH agonists	Goserelin acetate	
Progestins	Megestrol acetate Medroxyprogesterone acetate	
Androgens		
Non-selective aromatase inhibitors	Testolactone Aminoglutethimide	
Selective aromatase inhibitors	Formestane; Anastrozole; Letrozole; Fadrozole; Examestane	Low toxicity; now first choice for metastatic disease
Selective estrogen receptor modulators	Tamoxifen; Raloxifene; Arzoxifene	Useful in pre- and postmenopausal women
Estrogen receptor downregulators	Fulvestrant	Useful response in tamoxifen and aromatase inhibitor resistant patients

More about Tamoxifen

- **MOA of tamoxifen**:
 - **Partial Estrogen receptor antagonists** in breast; **block the binding of estrogen to estrogen receptor positive cells**.
- **Estrogen receptor agonists in bone**, preservation of bone mineral density.
- **Side effects** – see below:
 - **Raloxifene** has **NO increase in risk of endometrial Ca** and thromboembolism.



Newer Drugs in Breast Ca Treatment

- **Trastuzumab** (Herceptin), a monoclonal antibody that binds to **HER-2/neu receptors**, has proved effective in combination with chemotherapy in patients with **HER-2/neu** overexpressing metastatic and early breast cancer.
- **Lapatinib** is a newer oral targeted drug that works by inhibiting the Intracellular tyrosine kinases of the **endothelial growth factor and HER-2/neu receptors**. This drug is FDA-approved for the treatment of

trastuzumab-resistant **HER-2/neu**-positive metastatic breast cancer in combination with capecitabine, thus, a **completely oral regimen**.

Breast Cancer Surgery Terminologies

1. **Wide local excision**: Tumour along with 2cm of normal tissue is removed with an ellipse of skin over the lump
2. **Quadrantectomy**: Obsolete; quadrant containing the tumor is removed

3. **QUART: QUAdrantectomy + Axillary clearance + RadioTherapy** not popular and not practiced anymore.
4. **Simple Mastectomy:** All breast tissue + nipple areola complex + skin are removed with preservation of both pectoralis major and minor.
5. **Extended Simple Mastectomy:** Simple mastectomy + removal of level I axillary nodes.
6. **Modified Radical Mastectomy:** Simple mastectomy + removal of level I and level II axillary nodes.
7. **Halsted's Radical Mastectomy:** Simple mastectomy + removal of level I and level II axillary nodes + removal of both pectoralis major and minor but *it preserves* – Axillary nerve, Bell's nerve (long thoracic N to serratus anterior), Cephalic vein.
8. **Extended Radical Mastectomy:** Radical mastectomy + removal of internal mammary lymph nodes.
9. **Super Radical Mastectomy:** Radical mastectomy + internal mammary nodes + supraclavicular lymph node removal.

Mastectomy

- The traditional **radical mastectomy** (Haagenson, Stiles, and others) removes both pectoralis major and minor. Removing pectoralis major is mutilating, and has not been shown to produce any more survivors than operations which leave it, such as Patey's.
- In **Patey's mastectomy**, the breast and associated structures are removed en bloc and the **excised mass is composed of:**
 - The whole breast
 - A large portion of skin, the center of which overlies the tumour but which always includes the nipple
 - All of the fat, fascia and lymph nodes of the axilla
- The pectoralis minor muscle is either divided or retracted to gain access to the upper two thirds of the axilla.
- The **intercostal brachial nerves are usually divided in this operation without major sequelae** and the patient should be warned about sensation changes postoperatively (Only slight numbness of the medial aspect of upper arm would result).
- Note: **Intercostobrachial N.** is also injured during **sentinel lymph node biopsy**.

Structures that should be preserved in Patey's mastectomy

- The **axillary vein**.
- **Nerve to serratus anterior** (long thoracic nerve): if cut, winging of scapula results.
- **Nerve to latissimus dorsi** (thoracodorsal nerve): if cut, rotation and abduction of shoulder are weakened.

Modified Radical Mastoidectomy (MRM): Two Types

1. **Auchincloss MRM:** Both pectoralis major and minor are preserved with removal of level I and II axillary nodes only.
2. **Patey's MRM:** Pectoralis minor is removed with complete axillary clearance of nodes upto level III:
 - a. **Scanlon's modification of Patey's MRM:** Instead of removing pectoralis minor, the muscle is just divided so that level 3 nodes can be removed.

Breast Conservation

- **Breast-conserving treatments**, consisting of the removal of the primary tumor by some form of lumpectomy with or without irradiating the breast, result in a survival that is as good as (or slightly superior to) that after extensive surgical procedures, such as mastectomy or modified radical mastectomy, with or without further irradiation.

Contraindications for breast conservation

- Multicentric disease (i.e. disease in separate quadrants of breast).
- Extensive intraductal component related to locally invasive disease.
- Extensive in situ component/microcalcifications.
- Large tumor size relative to that of breast
- Women with a history of collagen-vascular disease
- Pregnancy (since radiation is contraindicated)
- Women who either do not have the motivation for breast conservation or do not have convenient access to radiation therapy

EXTRA EDGE

- **NOT** contraindications for breast conservation: Age, family history, axillary lymph nodes involved.
- **Milan Trial, NSABP trial, EORTC trial** - these compared Breast conserving therapy versus Mastectomy.

Breast Reconstruction

- **MC method** of breast reconstruction: **silicon implants**.
- **Surgical breast reconstruction** should never be done prior to radiotherapy.
- MC myocutaneous flap used is **TRAM** (transversus abdominis) flap.

MAMMOGRAPHY

- This is a **low energy (0.1cGy) X-ray** examination of the breast used as a **screening** and **diagnostic** tool.
- Specificity is 90% and positive predictive value is lower.
- Target materials used in anode in mamography are **Molybdenum** (MC used due to low voltage x-rays produced), tungsten and rhodium.

- In **young women, with dense breasts**, mammography is less sensitive than in older women with fatty breasts.
- The two **standard views** for screening in mamimography are cranio-caudal (CC) and mediolateral oblique views (MLO).
- **MLO view** images **greatest volume** of breast tissue including the upper outer quadrant and axillary tail of Spence.
- **CC view** provides better view of **medial aspect** of breast and permits **greater breast compression**.

Mammographic findings of DCIS

- Microcalcifications (**most characteristic**)
- Prominent ducts
- Mass
- Architectural changes

Mammographic signs of carcinoma

- **Clustered, fine or irregular calcifications** (malignant microcalcifications)—**MC**
- a mass with ill-defined or **spiculated** borders.
- distortion of adjacent breast stroma and skin thickening (**architectural distortion**)
- **Wide halo**; subcutaneous retromammary space is obliterated

Breast lesions containing fat

- Hamartoma (**fibroadenolipoma**): on mammography seen as **"breast within a breast"** appearance
- Lipoma: does not calcify
- Galactoceles: contains thick inspissated milk
- Fat necrosis: can calcify (**dystrophic calcification**) over time
- Oil cyst: localized form of fat necrosis

Breast lesions containing fat

- Intramammary lymph node (classically has a central fatty hilum)
- Rare lesions (steatocytoma multiplex, angiomyolipoma, liposarcoma)

Xeroradiography

- It is basically the same technically as mammography, except that the image is recorded on a **selenium-coated film** producing a **positive impression** to make it easier to the untrained eye.

BI-RADS

- BI-RADS = **Breast Imaging Reporting And Data System**.
- BI-RADS is a quality assurance tool designed to standardize mammography reporting, reduce confusion in breast imaging interpretations, and facilitate outcome monitoring:
 - BI-RADS 0 - **incomplete** - further imaging or information is required
 - BI-RADS I - **negative** - symmetrical and no masses, architectural disturbances or suspicious calcifications present.

- BI-RADS II - **benign** findings
- BI-RADS III - **probably benign** - short interval follow-up suggested.
- BI-RADS IV - **suspicious abnormality**:
 - BIRADS IVa - low level of suspicion for malignancy
 - BIRADS IVb - intermediate suspicion for malignancy
 - BI-RADS IVc - moderate suspicion for malignancy
- BI-RADS V - is **highly suggestive of malignancy** - action should be taken.
- BI-RADS VI - **known biopsy proven malignancy**.

MRI and Breast

- Breast MRI is the **best imaging** modality for the breasts of **women with implants**.
- Breast MRI can be useful **to distinguish scar from recurrence** in women who have had previous breast conservation therapy for cancer (BUT it is less accurate within nine months of radiotherapy).
- Breast MRI is becoming the **standard of care when a lobular cancer is diagnosed** to assess for multifocality and multicentricity and can be used to assess the extent of DCIS (ductal carcinoma in situ).
- It has proven to be useful as a **screening tool in high-risk women** (because of family history).
- It is **LESS USEFUL than ultrasound** in the management of the axilla in both primary breast cancer and recurrent.

Breast Cancer Trials

- Breast Cancer Prevention Trial (BCPT)
- Study of Tamoxifen and Raloxifene [STAR] trial.
- Milan Trial
- NSABP trial
- EORTC trial

VENOUS DISORDERS

Superficial Thrombophlebitis

Etiology

- **Venous catheter (MC)**
- Pregnant or postpartum women
- In individuals with varicose veins
- Thromboangiitis obliterans
- A/w trauma
- Following IV therapy with irritating solutions.
- Secondary to abdominal cancer such as carcinoma of the pancreas.

Clinically

- In **spontaneous superficial thrombophlebitis**, the **long saphenous vein** is **MC involved**.

- Dull pain, induration, redness, and tenderness along the course of a vein.
- The inflammatory reaction *generally subsides in 1–2 weeks*; a firm cord may remain for a much longer period.
- Edema of the extremity is **UNCOMMON**.
- Superficial thrombophlebitis may be a/w occult deep venous thrombosis (DVT) in about 20% of cases.

Treatment

- Local heat and NSAIDs are usually effective in limiting the process.
- If the induration is extensive or is progressing toward the saphenofemoral junction (leg) or cephalo-axillary junction (arm), ligation and division of the vein at the junction of the deep and superficial veins is indicated.
- Anticoagulation therapy is usually **NOT** indicated unless the disease is rapidly progressing or there is concern for extension into the deep system.

Septic superficial thrombophlebitis

- This is an **intravascular abscess** and **may require excision of the involved vein** in order to control the infection.
- **MC** by *Staphylococcus aureus*.
- Start broad-spectrum **antibiotics** immediately

Contd...

Contd...

Septic superficial thrombophlebitis

- If cultures are positive, therapy should be continued for 7–10 days or for 4–6 weeks if complicating endocarditis cannot be excluded.
- **Heparin** may be **required**.

VARICOSE VEINS

- Varicose veins are defined as **dilated, usually tortuous, subcutaneous veins ≥ 3 mm in diameter** measured in the upright position with demonstrable reflux
- **Risk factors:**
 - Females
 - Increasing age
 - Increasing height and BMI
 - Pregnancy
 - Positive family history
 - Prolonged standing, constipation, smokers (inconclusive evidence).

Classification

- The **CEAP** (Clinical – Etiology – Anatomy – Pathophysiology) classification for chronic venous disorders is widely utilised.

Clinical classification	Etiologic classification	Anatomical classification	Pathophysiological classification
C0: No signs of venous disease	Ec: Congenital	As: Superficial veins	Pr: Reflux
C1: Telangiectasia or reticular veins	Ep: Primary	Ap: Perforator veins	Po: Obstruction
C2: Varicose veins	Es: Secondary (post-thrombotic)	Ad: Deep veins	Pro: Reflux and obstruction
C3: Edema	En: no venous cause identified	An: No venous location identified	Pn: No venous pathophysiology identifiable
C4a: Pigmentation or eczema			
C4b: Lipodermatosclerosis or atrophie blanche			
C5: Healed venous ulcer			
C6: Active venous ulcer			

Each clinical class is further characterised by a subscript depending upon whether the patient is symptomatic (S) or asymptomatic (A) e.g. C2S.

Clinical Features

- **MC symptom** is *aching or heaviness*, which typically increases through-out the day or with prolonged standing and is relieved by elevation or compression hosiery.
- Other less common symptoms include *ankle swelling and itching* while other complications are mentioned below.
- **Tortuous dilated subcutaneous veins** are present - these are confined to the long and lesser saphenous

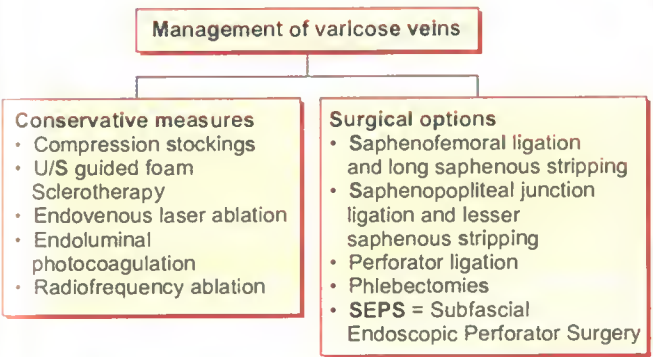
systems in approximately 60 and 20 per cent of cases, respectively.

- **Telangiectasia**, (spider veins, thread veins, hyphen webs): which are essentially a confluence of dilated intradermal venules <1 mm in diameter.
- **Reticular veins**: Reticular veins are dilated, subdermal veins, 1–3 mm in diameter.
- In **saphena varix**, there is a large groin varicosity which presents as a (usually painless) lump, emergent when standing and disappearing when recumbent. Gentle

palpation over the varix during coughing may elicit a thrill

- **Atrophie blanche** is localised white atrophic skin frequently surrounded by dilated capillaries and hyperpigmentation, usually seen around the ankle.
- **Corona phlebectasia** are fan-shaped patterns of small intradermal veins on the medial or lateral aspects of the ankle or foot. Synonyms include **malleolar or ankle flares**
- **Pigmentation**
- **Superficial thrombophlebitis**
- **Eczema**
- **Dependant pitting edema**
- **Lipodermatosclerosis**
- **Ulceration**

Investigations



Patient factors	Disease or surgical procedure	Thrombophilia
<ul style="list-style-type: none">• Age• Obesity• Varicose veins• Immobility• Pregnancy• Puerperium• High-dose oestrogen therapy• Previous deep vein thrombosis or pulmonary embolism• Thrombophilia (see right-most column)	<ul style="list-style-type: none">• Trauma or surgery, especially of pelvis, hip and lower limb• Malignancy, especially pelvic, and abdominal metastatic• Heart failure• Recent myocardial infarction• Paralysis of lower limb(s) infection• Inflammatory bowel disease• Nephrotic syndrome• Polycythaemia• Paraproteinaemia• Paroxysmal nocturnal haemoglobinuria antibody or lupus anticoagulant• Behcet's disease• Homocystinaemia	<ul style="list-style-type: none">• Congenital: Deficiency of antithrombin III, protein C or protein S Antiphospholipid antibody or lupus anticoagulant• Factor V Leiden gene defect or activated protein C resistance• Dysfibrinogenaemias• Acquired: Antiphospholipid antibody or lupus anticoagulant

- Investigation of choice: **B mode Duplex Doppler ultrasound** imaging (7.5–13 MHz)
- The scan should begin in the groin, using a transverse view to identify the long saphenous vein and common femoral vein lying medial to the common femoral artery (the '**Mickey Mouse**' sign).
- Saphenofemoral junction (SFJ) competence is assessed in the transverse view and potential destinations for reflux including the greater or long saphenous vein (LSV), the accessory anterior saphenous vein and other major thigh tributaries superficial to the saphenous fascia are noted.
- The full length of the LSV within its fascial compartment, known as the '**saphenous eye**', should be examined, and its diameter measured just below the SFJ, mid-thigh, above and below the knee joint, mid-calf and ankle.

DEEP VEIN THROMBOSIS (DVT)

Risk Factors for DVT

- MC presentation of a DVT is **pain and swelling, especially in the calf** (usually in one lower limb; however, bilateral DVT are common, occurring in up to 30%).
- Some patients have no symptoms of thrombosis and may first present with **signs of a pulmonary embolism**, e.g. pleuritic chest pain, haemoptysis and shortness of breath.
- Sometimes the **leg appears cellulitic** and, very occasionally, it may be **white (phlegmasia alba dolens)**

or *cyanosed (phlegmasia cerulea dolens)*. Clinical examination for DVT is unreliable. Physical signs may also be absent.

- *Mild pitting oedema of the ankle, dilated surface veins, a stiff calf and tenderness* over the course of the deep veins may be present.
- **Homans' sign** – resistance (not pain) of the calf muscles to forcible dorsiflexion is not specific and should not be elicited.
 - Patients who are confirmed to have a deep vein thrombosis on duplex imaging should be started on *subcutaneous low molecular weight heparin* and *rapidly anticoagulated with warfarin* unless there is a specific contraindication.

ARTERIAL DISORDERS

Critical Limb Ischemia (CLI)

- **Rest pain (Night pain)** occurs with the leg at rest. Pain is worse in horizontal position (sleeping) and relieved by hanging the foot out of bed or sleeping in a chair.
- CLI is defined as:
 - Rest (night) pain *requiring opiate analgesia* and/or tissue loss (ulceration or gangrene) present for *more than 2 weeks* in the presence of an *ankle blood pressure of less than 50 mmHg*
 - ABPI < 0.5.

Intermittent Claudication (IC)

- A **cramp like pain** felt in the muscles that is:
 - **Precipitated** by walking.
 - **Relieved** by standing still (*unlike pseudoclaudication* in lumbar IV disc nerve compression OR osteoarthritis of spine or spinal stenosis)
 - NOT present on taking the first step (*unlike osteoarthritis*)
- In **intermittent claudication (IC)**, Ankle: Brachial Pressure Index (ABPI) = **0.5 – 0.9**.
- Pain of IC is **MC felt in the calf** since the **superficial femoral artery** is MC involved; BUT it can affect the thigh or buttock if the iliac arteries are involved.
- **Leriche's syndrome** = buttock claudication + sexual **impotence** (aortoiliac obstruction).
- In **aorto-iliac obstruction**: Femoral and distal pulses **absent** in both limbs AND **bruit** over aorto-iliac region.

Gangrene

- **Gangrene** refers to death of macroscopic portions of tissue which turn black because of the breakdown of haemoglobin and the formation of **iron sulphide**.
- It usually affects the most distal part of a limb because of arterial obstruction (from thrombosis, embolism or arteritis).
- **Dry gangrene** occurs when the tissues are desiccated by gradual slowing of the bloodstream; it is typically the result of atheromatous occlusion of arteries.
- **Wet gangrene** occurs when superadded infection and putrefaction are present.
- **Crepitus** may be palpated as a result of infection by gas-forming organisms commonly in diabetic foot problems.
- A **zone of demarcation** between the truly viable and the dead or dying tissue will eventually appear.
- Separation is achieved by the development of a layer of **granulation tissue**, which forms between the dead and the living parts.
- Treatment is by **debridement of devitalised tissue** and **amputation**.
- Specific types of gangrene are **diabetic gangrene, frostbite** and **bedsores**.

Ankle Brachial Pressure Index (ABPI)

- The ABPI is the **ratio of systolic pressure at the ankle to that in the arm**.
- The highest pressure in the *dorsalis pedis, posterior tibial or peroneal artery* serves as the *numerator*, with the highest brachial systolic pressure being the denominator.

ABPI value	What it means
1.0	Resting/healthy person
0.5 - 0.9	Claudication
< 0.5	Suggests rest pain/critical limb ischemia
< 0.3	Imminent necrosis

EXTRA EDGE

- **False high ABPI** may be seen in **diabetes, atherosclerosis and chronic renal disease** due to **calcification of arteries**.

Ultrasonography of Deep Vein Thrombosis

- Primary criterion: **Loss of vein compressibility**.

- **"Wink" sign negative**: When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure from the ultrasound transducer - this creates the illusion of a "wink".
- Directly visualized thrombus - appears **homogeneous with low echogenicity**
- **Blunted Doppler** flow response to calf compression.

Indications for Carotid Endarterectomy in Symptomatic Patients

70% or greater carotid stenosis and:

- **Ipsilateral amaurosis fugax** or monocular blindness
- **Contralateral facial paralysis** or paraesthesia
- **Arm/leg paralysis** or paraesthesia
- **Hemianopia**
- **Dysphasia** (if dominant hemisphere)
- Sensory or visual inattention/neglect.

Acute Arterial Occlusion

- **Sudden occlusion** of an artery is usually caused **MC** by an **embolus**.

PATIENT SAFETY

PATIENT SAFETY, QUALITY IMPROVEMENT

- Human factor (HF) is the study of the inter-relationships between humans, the tools they work with and the environment in which they work.
- The SHELL model was designed to understand these relationships - **Software; Hardware; Environment; Livewares**.
- **Heinrich's safety pyramid**: This accident pyramid proposes that for every 300 near misses, there are 29 minor injuries and one major injury.
- **James Reason's Swiss Cheese model of accident causation** (used in aviation, nuclear power industries

- The symptoms and signs of embolism (five Ps) - with **Pain, Pallor, Paralysis, loss of Pulsation and Paraesthesia** (or anaesthesia)
- **Embolectomy** is done with the help of a **Fogarty balloon catheter**.

Thromboangiitis Obliterans (TAO, Buerger's Disease)

- TAO is characterised by **occlusive** disease of **small- and medium-sized arteries** (plantar, tibial, radial, etc.), **thrombophlebitis of the superficial or deep veins**, and **Raynaud's syndrome**.
- It occurs **MC in male smokers**, usually under the age of 30 years.
- Histologically, there are inflammatory changes in the walls of arteries and veins, leading to thrombosis.
- Treatment is **total abstinence from smoking**, which arrests, but does not reverse, the disease. Established arterial occlusions are treated as for atheromatous disease, but amputations may eventually be required.

and healthcare) takes Heinrich's concept forward and proposes the notion of active failures and latent conditions.

- The **Haddon Matrix** is the MC used paradigm in the **injury prevention field**. The "Haddon Matrix" is a table showing the host, agent and environmental factors involved, set against the time sequence of an incident.
- **LEAN** and **Six Sigma** are **quality improvement** tools used in healthcare.
- **DMAIC** in Six Sigma stands for **Define, Measure, Analyse, Improve, Control**.

Patient Safety Incidents

Term	Definition
Adverse event	An incident that results in harm to the patient
Near-miss event	An incident that could have resulted in unwanted consequences but did not, either due by chance or due to a timely intervention preventing the event from reaching the patient (Ex: Prophylactic cephalosporins was to be given, BUT it was stopped in the nick of time, since the nurse realised that the patient has known allergy to penicillin)
No-harm event	An incident that occurs and reaches the patient, but results in no injury to the patient. Harm is avoided by chance or due to mitigating circumstances (Ex: In the same patient mentioned above, the cephalosporin injection was given, BUT luckily it did not result in any harm to the patient)



SURGICAL SAFETY CHECKLIST (FIRST EDITION)

Before induction of anaesthesia ▶▶▶▶▶▶▶▶

Before skin incision ▶▶▶▶▶▶▶▶▶▶

Before patient leaves operating room

SIGN IN

- ☐ PATIENT HAS CONFIRMED
 - IDENTITY
 - SITE
 - PROCEDURE
 - CONSENT
- ☐ SITE MARKED/NOT APPLICABLE
- ☐ ANAESTHESIA SAFETY CHECK COMPLETED
- ☐ PULSE OXIMETER ON PATIENT AND FUNCTIONING
- DOES PATIENT HAVE A:
 - KNOWN ALLERGY?
 - ☐ NO
 - ☐ YES
 - DIFFICULT AIRWAY/ASPIRATION RISK?
 - ☐ NO
 - ☐ YES, AND EQUIPMENT/ASSISTANCE AVAILABLE
 - RISK OF >500ML BLOOD LOSS (7ML/KG IN CHILDREN)?
 - ☐ NO
 - ☐ YES, AND ADEQUATE INTRAVENOUS ACCESS AND FLUIDS PLANNED

TIME OUT

- ☐ CONFIRM ALL TEAM MEMBERS HAVE INTRODUCED THEMSELVES BY NAME AND ROLE
- ☐ SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE VERBALLY CONFIRM
 - PATIENT
 - SITE
 - PROCEDURE
- ANTICIPATED CRITICAL EVENTS
 - ☐ SURGEON REVIEWS: WHAT ARE THE CRITICAL OR UNEXPECTED STEPS, OPERATIVE DURATION, ANTICIPATED BLOOD LOSS?
 - ☐ ANAESTHESIA TEAM REVIEWS: ARE THERE ANY PATIENT-SPECIFIC CONCERNS?
 - ☐ NURSING TEAM REVIEWS: HAS STERILITY (INCLUDING INDICATOR RESULTS) BEEN CONFIRMED? ARE THERE EQUIPMENT ISSUES OR ANY CONCERNS?
- HAS ANTIBIOTIC PROPHYLAXIS BEEN GIVEN WITHIN THE LAST 60 MINUTES?
 - ☐ YES
 - ☐ NOT APPLICABLE
- IS ESSENTIAL IMAGING DISPLAYED?
 - ☐ YES
 - ☐ NOT APPLICABLE

SIGN OUT

- NURSE VERBALLY CONFIRMS WITH THE TEAM:
 - ☐ THE NAME OF THE PROCEDURE RECORDED
 - ☐ THAT INSTRUMENT, SPONGE AND NEEDLE COUNTS ARE CORRECT (OR NOT APPLICABLE)
 - ☐ HOW THE SPECIMEN IS LABELLED (INCLUDING PATIENT NAME)
 - ☐ WHETHER THERE ARE ANY EQUIPMENT PROBLEMS TO BE ADDRESSED
- ☐ SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE REVIEW THE KEY CONCERNS FOR RECOVERY AND MANAGEMENT OF THIS PATIENT

FEW SCORING SYSTEMS

Glasgow Coma Scale (GCS)

Eye opening (E)	Verbal response (V)	Motor response (M)
Spontaneous	4 Oriented	5 Obeys command
To Voice	3 Confused	4 Locates pain
To pain	2 Inappropriate words	3 Withdraws (pain)
None	1 Incomprehensible sounds	2 Flexion - abnormal (pain) - <i>decorticate</i> posturing (C=3rd letter, M3)
	None	1 Extension (pain) - <i>decerebrate</i> posturing (B=2nd letter, M2)
		None

Note: GCS maximum score = 15; GCS minimum score = 3.

TRAUMA

Trauma Score: Includes

- GCS score, respiratory rate, respiratory expansion, systolic BP, capillary refill.
- NOT accurate in patients with severe head injuries – hence replaced by the revised trauma score.

Revised Trauma Score (RTS)

- Respiratory rate, Systolic BP, GCS score

Abbreviated Injury scale (AIS)

- An anatomic scoring system designed to provide a reasonably accurate means of ranking the severity of injury. 6 body regions included are: head, neck, thorax, abdomen, spine and extremities.

Injury Severity Scores (ISS)

- AIS score squared in the 3 most severely injured body systems

Trauma Injury severity score (TRISS)

- **TRISS** = ISS + RTS + patients age

Contd...

Contd...

Score for extremity injury (limbs)

- **MESS** = Mangled Extremity Severity Score (includes skeletal/soft tissue injury), Limb ischemia, Shock, Age.
- **LSI** = Limb Salvage Index
- **NISSSA** = Nerve injury, Ischemia, Soft tissue, Skeletal injury, Shock and Age (modification of MESS)

APACHE II

Acute Physiology Assessment and Chronic Health Evaluation system

SAPS 2

Simplified Acute Physiology Score

CRAMS

Circulation, Respiration, Abdomen, Motor, Speech scale

cABCDE of major trauma care (Primary Survey)

- **c** (control of massive external hemorrhage)
- **A** (Airway maintenance cervical spine protection)
- **B** (Breathing and ventilation)
- **C** (Circulation with haemorrhage control; apply a pelvic binder until pelvic fracture is excluded)
- **D** (Disability: neurological status)
- **E** (Exposure - Assess for other injuries).

EXTRA EDGE

- **Glasgow Outcome Score (GOS)**: Good recovery,5; Moderate disability,4; Severe disability,3; Persistent vegetative state,2; Dead,1.
- **NICE guidelines** for **CT scan in head injury** has been mentioned in radiodiagnosis chapter (Pg 1183).
- **TRIAGE** color codes has been mentioned in PSM chapter (Pg 478).

Classification of Blast injuries

Classification	Type of Injury	Examples
Primary	Over-pressure from blast	<i>Tympanic membrane injury (MC)</i> ; blast lung; interstitial blast injury
Secondary	Penetrating / fragmentation	All penetrating injuries
Tertiary	Blunt	Blunt and crush injuries; traumatic amputation
Quaternary	Miscellaneous	Burns, inhalational injury
Quinary	Effect of device additions	Radiation sickness, infection

OTHER HIGH YIELD SURGERY TOPICS

SIGNS

- Auenbrugger's sign**: An epigastric prominence seen in cases of marked *pericardial effusion*.
- Ballance's sign**: The presence of a dull percussion note in both flanks, constant on the left side but shifting with change of position on the right, said to indicate *ruptured spleen*; the dullness is due to the presence of blood, fluid on the right side but coagulated on the left.
- Battle's sign**: Postauricular ecchymosis in cases of *fracture of the base of the skull*.
- Branham's sign**: Slowing of the heart rate following compression or excision of an *arteriovenous fistula*.
- Bryant's sign**: Abnormal position of axillary folds in *dislocation of the shoulder*.
- Carvallo's sign**: Increase in the intensity of the pansystolic murmur of *tricuspid regurgitation* during or at the end of inspiration.
- Cruveilhier's sign**: Caput *medusae*.
- Cullen's sign**: Periumbilical darkening of the skin from blood, as of intraperitoneal hemorrhage especially in *ruptured ectopic pregnancy*.

- Dance's sign**: A slight retraction in the neighbourhood of the right iliac fossa in some cases of *intussusception*.
- Ewart's sign**, **Pins's sign**: In large *pericardial effusions*, an area of dullness with bronchial breathing and bronchophony below the angle of the left scapula.
- Faget's sign**: A slow pulse with an elevated temperature, often seen in *yellow fever*.
- Grey Turner's sign**: Local areas of discoloration about the umbilicus and in the region of the loins, in *acute hemorrhagic pancreatitis*.
- Hamman's sign**: Crunching, rasping sound, synchronous with heart beat, heard over the precordium and sometimes at a distance from the chest in *pneumomediastinum*.
- Kehr's sign**: Violent pain in the left shoulder in a case of *rupture of the spleen*.
- Landolff's sign**: Systolic contraction and diastolic dilation of the pupil, seen in *aortic insufficiency*.
- Macewen's sign**: Percussion of the skull gives a cracked-pot sound in cases of *hydrocephalus*.
- Wreden's sign**: In the case of a stillborn child a gelatinous material more or less completely fills the *external auditory meatus*.

18. **Pemberton's sign:** Large **retrosternal goiters** can cause venous distention over the neck and difficulty breathing, especially when the arms are raised.
19. **Stemmer's sign:** A diagnostic test that involves pinching the skin on the upper surface of the toe (usually second toe) or fingers. If a fold of skin can be pinched and lifted up at the base of the second toe or middle finger, the Stemmer sign is negative. Stemmer sign is positive and indicative of **lymphedema** when a skin fold cannot be lifted, but can only be grasped as a lump of tissue.

FEW NAMED SURGERIES

Surgery/surgeon name	Performed for
Heller's myotomy	Achalasia cardia
Thiersch's, Delorome's, Altemier's operation	Full thickness prolapse of the rectum
Lord's and Jaboulay's	Hydrocele
Whipple's	Pancreaticoduodenectomy for Ca head of pancreas
Billroth I and II	Gastrectomy for peptic ulcers
Kasai procedure	Extrahepatic biliary atresia, type 2 and 3
Notaras	Lateral anal sphincterotomy for anal fiss
Kashima surgery	Vocal cord surgery

IMPORTANT NAMED LYMPH NODES

Rotter's nodes	Interpectoral nodes (Ca breast)
Rouvier nodes	Retropharyngeal nodes (Ca Nasopharynx)
Delphian nodes	Pre-cricoid/Pre-tracheal/Pre-laryngeal lymph nodes
Irish nodes	Nodes in left axilla (CA stomach)
Sister Mary Joseph nodes	Periumbilical metastatic cutaneous nodules
Virchow nodes	Left supraclavicular node
Cloquet node	Femoral canal node
LN of Lund	Cystic lymph node
Krouse Lymph node	Jugular fossa lymph node

SURGICAL POSITIONS

Supine Position

A.k.a **dorsal recumbent** position; **The most common surgical position** and produces the least hemodynamic and ventilatory changes

- Variations of the supine position include:
 - **Lawn-chair** position
 - **Frog-leg** position

Trendelenburg Position

- A supine position with the **table tilted head down** so that **head is lower than the feet**.
- Used for **surgery on the lower abdomen** and pelvis.
- Also indicated for patients who develop **hypovolemic shock**.

Reverse Trendelenburg Position

- A supine position with the **table tilted foot down**
- Used for **head and neck procedures**.

Lithotomy Position

- An extreme **variation of the supine position** in which the **legs are elevated abducted and supported in stirrups**.
- Used for procedures involving the **perineum, pelvic organs and genitalia**.

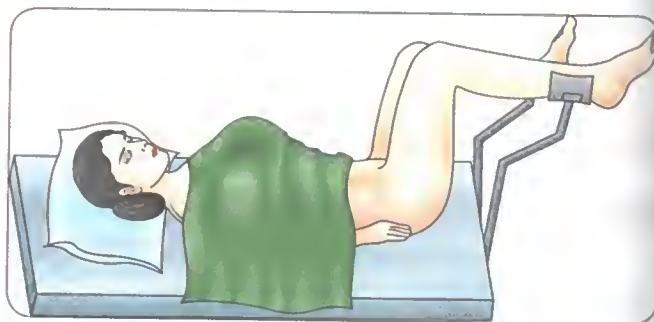


Fig. 22.29: Lithotomy position



Fig. 22.30: Sim's position

TRIANGLES IN SURGERY

- Calot's triangle**
 - Superiorly: Inferior border of liver
 - Medially: common hepatic duct
 - Laterally: cystic duct
 - Significance: cystic artery runs across the triangle from medial to lateral side

Contd...

Contd...

- Lumbar triangle of Petit**
 - Anteriorly: Posterior border of external oblique
 - Posteriorly: Anterior border of latissimus dorsi
 - Below: Iliac crest
 - Floor: Internal oblique
 - Significance: Site of lumbar hernia
- Triangle of safety**
 - Insertion of chest drain** is indicated when there is air (pneumothorax) or fluid (pyothorax, effusion) in the pleural cavity.
 - The site of insertion is in the **triangle of safety** which lies:
 - Anterior to the midaxillary line
 - Above the level of the nipple
 - Below and lateral to the pectoralis major muscle, this will ideally find the **fifth intercostal space**
 - If the **meniscus** of the fluid in the **chest drain** is **not swinging** during the respiratory process, it means that the **chest drain is blocked**.

VASCULAR MALFORMATIONS

- A **hemangioma** is a developmental malformation of blood vessels and not a typical tumour. So it is considered to be an example of '**hamartoma**'. Such theory can be explained by the observations that – **Hemangioma is often present since birth; it never turns malignant**.
- Hemangiomas may occur anywhere in the body though it is more common in the skin and subcutaneous tissues.

Capillary Hemangioma

Strawberry Angioma

- A red mark (angioma) is noticed **1-3 months after birth**, which gradually **increases in size for a few months** till it takes a typical strawberry appearance.
- "Sign of emptying"**: Strawberry angioma is soft and sustained pressure will squeeze most of the blood out of the hemangioma leaving it collapsed. As soon as the pressure is released refilling occurs quickly.
- After the first birthday, the angioma gradually regresses in size and **involution** may be complete by the age of **7-8 years**.
- Systemic associations**:
 - High output heart failure,
 - **Kasabach-Merritt** syndrome (**thrombocytopenia, anemia, low levels of coagulant factors**) and
 - **Mafucci** syndrome (skin hemangiomas, enchondroma of hands, feet and long bones as well as bowing of long bones).

Port Wine Stain (Naevus Flammeus)

- It is usually **present since birth** and **persists for life**. It is common on the **face and scalp**, neck and buttock. The lesion contains many dilated blood vessels. Does **NOT** blanch on pressure.
- Sturge-Weber syndrome** is a/w **facial port wine stain**
- Treatment** of choice: **pulsed dye laser**.

Salmon Patch

- Also called "**stork bites**", "**angel's kisses**". It is **present since birth**; usually **disappears before the first birthday**.
- It is mostly seen over the **forehead or occiput** or **anywhere in the midline** of the body.

Cavernous Hemangioma

- It is composed of **large vascular spaces**. It is a soft compressible **mauveish-blue swelling** which may vary slightly in size from day to day.
- Common sites are the face, cheek, ears; mucous membrane of lips, mouth and tongue; liver, kidney and brain. It **does not** show any tendency to spontaneous involution.

Glomus Tumour

- Glomus tumors are **benign** neoplasms that differentiate toward **modified smooth muscle cells** called glomus cells.
- They arise from the arterial portion of the glomus body (**Sucquet-Hoyer canal**), which is an arteriovenous shunt in the dermis that contributes to **temperature regulation**.
- The MC location for glomus tumors is the **subungual areas** (below the nails) of the **fingers and toes**; seen as **blue-purple**, often **blanchable** papules or nodules.
- The MC adverse effect is **pain**, usually associated with solitary lesions
- Two useful signs for diagnosing glomus tumors include **Hildreth sign**, which is disappearance of pain after application of a tourniquet proximally on the arm, and the **Love test**, which consists of eliciting pain by applying pressure to a precise area with the tip of a pencil. These are most helpful for diagnosing solitary painful subungual glomus tumors.
- The **treatment** of choice is **surgical excision** of the tumour.

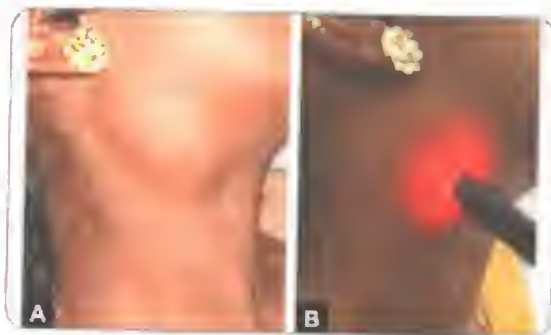
Pyogenic Granuloma

- Pyogenic granuloma is a **benign vascular lesion** of the skin and mucosa; a misnamed entity that is **neither infectious nor granulomatous!!**.
- It does **not** appear to be a hamartomatous malformation as it characteristically **appears over a few days** or a week and **disappears after several weeks** or at the most, a few months.
- The lesion usually occurs in **children and young adults** as a **solitary glistening red papule or nodule** that is prone to bleeding and ulceration, seen most often on the **fingers and toes, and head and neck**.
- Pyogenic granuloma often arises in pregnancy (or rarely with oral contraceptive usage), particularly on the gingiva or elsewhere in the oral mucosa, and then is termed the "**pregnancy tumor**".
- Medication induced subtypes **is due to** - retinoid (**isotretinoin**) and protease inhibitor (**indinavir**).

NECK

Branchial Cyst

- Branchial cyst** develops from the **vestigial remnants of the second branchial cleft** and the cyst is usually **lined by squamous epithelium** and its contents are either clear fluid or like toothpaste. Mnemonic: ("**Syst is from Second**").
- Usually found at junction of **upper and middle one third of sternomastoid muscle** at its anterior border.
- Fluctuant, transilluminant** swelling.
- If cyst gets **infected** a erythematous and tender and may be difficult to differentiate from TB abscess.
- Diagnosis by FNAC and ultrasound.
- Treatment by **complete excision**.
- TAKE CARE to avoid damage to:
 - Common carotid artery
 - Glossopharyngeal nerve (IX)
 - Spinal accessory nerve (XI)
 - Hypoglossal nerve (XII)



Figs. 22.31A and B: Branchial cyst. It is only occasionally transilluminant

Branchial Fistula

- Branchial fistula** represents **persistent second branchial cleft**.
- External orifice in **lower third of neck** near anterior border of sternomastoid; internal orifice on the **anterior aspect of the posterior faucial pillar just behind the tonsil**.
- Lined by **ciliated columnar epithelium** a mucoid or mucopurulent discharge.
- Complete excision** required.

Neck Dissection

- Classical Radical neck dissection, CRND (Crile):**
 - It involves removal of lymph nodes levels I-V; the internal jugular vein (IJV), the spinal accessory nerve (SAN), the submandibular gland and the sternocleidomastoid muscle (SCM).
 - The main disability that follows the operation is weakness and drooping of the shoulder due to paralysis of the trapezius muscle (due to excision of SAN).
- Extended RND (ERND):**
 - Removal of all structures in a CRND + **removal of further lymph node group**, e.g. level VI, level VII or retropharyngeal or parapharyngeal nodes lymph nodes OR **non-lymphatic structures** like part of the mandible, parotid, mastoid tip, digastric muscle, prevertebral fascia, hypogastric muscle, external carotid artery as well as the skin.
- Modified Radical neck dissection, MRND:**
 - Similar to above radical neck dissection BUT it saves one or more of the following structures: **spinal accessory nerve (SAN); internal jugular vein (IJV)** and **sternocleidomastoid muscle (SCM)**.
 - Type 1 MRND: SAN preserved
 - Type 2 MRND: SAN and SCM preserved
 - Type 3 MRND: SAN, SCM and IJV preserved.
- Selective Neck Dissection**
 - In this type of dissection, **one or more of the major lymph node groups is preserved** along with the SCM, SAN and IJV.

Pendred syndrome

- Mutation of the **PENDRIN gene** (chromosome 7q) causes **Pendred syndrome**, an **autosomal recessive** disorder characterized by:
 - Defective organification of iodine
 - Goiter**
 - Sensorineural deafness** (typically a/w a malformation of the inner ear bony labyrinth, referred to as **Mondini cochlea**).

MALE GENITALIA

Torsion of Testis

- Torsion of the testis** (or more correctly, **torsion of the spermatic cord**), is a **surgical emergency** because it causes strangulation of gonadal blood supply with subsequent testicular necrosis and atrophy.
- Clinically:**
 - Acute scrotal swelling in children** indicates **torsion of the testis until proven otherwise**.
 - Tremendous amount of pain** is characteristic; dizziness and nausea may be present.
 - A physical examination may reveal a **swollen, tender, high-riding testis**.
- Treatment:**
 - Prompt exploration, untwisting and fixation** is the only way to save the torqued testis. The patient should be counseled and consented for orchidectomy before exploration.
 - The anatomic abnormality is bilateral and the **contralateral testis should also be fixed**.
- Prehn's sign:** **Elevation of the scrotum** usually **relieves pain in epididymo-orchitis**, but increases the pain in torsion of the testis (spermatic cord).
- Deming's sign:** **tender lump at superficial inguinal ring** (high positioned testis).
- Angell's sign:** **Opposite testis lies horizontally** (because of mesorchium).

Testicular Torsion vs Epididymitis

	Testicular torsion	Epididymitis
Age	< 30 years (usually prepubertal)	> 30 years
Appearance	Testes may be elevated into the inguinal canal; swelling	Swollen testis, overlying erythema, urethral discharge/urethritis, prostatitis
Prehn's sign	Pain stays the same or worsens	Pain decreases with testicular elevation
Treatment	Immediate surgery to salvage testis; surgical orchiopexy for both testis	Antibiotics (cotrimoxazole or ciprofloxacin)

Treatment of Hydroceles

Congenital Hydroceles

- Need herniotomy** as they do not resolve spontaneously.

Acquired Hydrocele

- Lords operation:** is suitable when the **sac is reasonably thin walled**.
- Jaboulay's procedure:** **Eversion of the testis** with **placement of the testis in a pouch** prepared by dissection in the fascial planes of the scrotum.

CAUSES OF LYMPHEDEMA

Primary lymphedema	Secondary lymphedema
Developmental abnormality of lymphatic flow; has 3 forms but all may not be clinically evident at birth	Acquired abnormality of lymphatic flow
<ul style="list-style-type: none"> Congenital lymphedema: present at birth; MC in females; MC in Lower limb; 2/3 cases are bilateral; may improve with age Lymphedema praecox (MC form of primary lymphedema): appears at puberty; MC in females; 70% affects unilateral lower limb (L>R) Lymphedema tarda: presents at age 35 or older 	<ul style="list-style-type: none"> Neoplasms Post surgical obstruction Burns Insect bites Infection Surgery Trauma

ORGAN TRANSPLANTATION

"FIRSTS" in Organ Transplantation

Organ transplant	By (Name)	Date
Corneal	Edward Zim	1906
Kidney	RH Lawler	1950
Liver	Thomas Starzl	1961
Lung transplant	James Hardy	1963
Pancreas	Richard Lillehl	1966
Heart	Christiaan Barnard	1967
Heart Lung	Denton Cooley	1968

Also Know: **Dr. Med Erich Mühe** of Böblingen, Germany, performed the **first laparoscopic cholecystectomy** on September 12, 1985.

Organs and tissues that can be transplanted at present

- Kidney
- Lung
- Liver
- Pancreas and islet cells of langerhans
- Heart and heart valves
- Cornea
- Middle ear
- Skin
- Bone/tendons
- Bone marrow
- Blood vessels (MC saphenous vein)

Maximum and Optimal Cold Storage Times

Organ	Optimal storage time (hours)	Safe maximum storage time (hours)
Kidney	<18°	36°
Liver	<12	18
Pancreas	<10	18
Small intestine	<4	6
Heart	<3°	6
Lung	<3°	8

Modified Maastricht Classification

- Organ donation *after the cardiac death of donors* is graded as per the modified Maastricht Classification.
- **Category 1, 2, 5** are considered **uncontrolled** donation- i.e., which require maintenance of organ perfusion and rapid cooling by either post mortem CPR or cardio-pulmonary bypass with external oxygenation.
- **Category 3, 4** are considered **controlled** donation

Category	Clinical description	Type
1	Dead on Arrival	Uncontrolled
2	Unsuccessful resuscitation (arrest occurs unexpectedly and you are not able to revive the patient)	Uncontrolled
3	Anticipated cardiac arrest (after removal of ventilator support in a hospitalised patient)	Controlled
4	Cardiac arrest in brain dead donor	Controlled
5	Unexpected arrest in ICU patient	Uncontrolled

ADDITIONAL HIGH YIELD POINTS

- **Cleft lip** reconstruction is generally performed at approximately 3 -6 months of age.
- **Cleft palate** reconstruction is performed between 6-18 mopnth's age to aid in normal speech development.
- **Rhytidectomy** (face-lift) is a procedure that undermines the skin of the face and neck.
- **Dermabrasion** is the physical abrasion of the skin commonly used to treat acne scarring.
- **Blepharoplasty** is used to treat baggy eyelids.
- **Rhinoplasty** corrects congenital or acquired nasal defects.
- **Liposuction** is used to remove localised deposits of fat. It is not a weight reduction procedure.
- **MC soft tissue sarcoma** in adult is **Malignant fibrous histiocytoma**; MC in **thigh**
- **MC soft tissue sarcoma** in children is **rhabdomyosarcoma**
- **Pulmonary contusion** is the MC lung injury seen with thoracic trauma.
- **Aortic transection** is usually the result of a major **deceleration** chest injury.
- The **right ventricle** situated substernally is **most vulnerable to injury** in blunt/penetrating chest trauma.
- **Massive hemoptysis** is defined as bleeding **>600 ml over 24 hours**. TB accounts for majority of cases.
- Diagnosis of pneumothorax is confirmed by erect **PA view** chest X-ray. Standard films are taken in inspiration, but a small pneumothorax is accentuated by an **expiratory film**.
- The **pleural space** is a potential space between the parietal and visceral pleura that contains only about **5 ml of pleural fluid** at any one time.
- **Pleurodesis**: aim of this technique is to obliterate the pleural space by creating an inflammatory reaction between the visceral and parietal pleura using various agents such as - **Sclerosants** (tetracycline, talc) and **Cytostatic agents** (C.parvum, IL-2, cisplatin, 5-fluorouracil).
- The classic aetiology of **empyema** and still probably the MC is **post-pneumonic**.
- **Scimitar syndrome**: The right pulmonary vein drains into the inferior vena cava (IVC) or right atrium, leading to a characteristic radiographic appearance.
- **Odynophagia** is sharp substernal *pain on swallowing* that may limit oral intake. It is MC a/w **infectious oesophagitis** due to Candida, herpesviruses, or cytomegalovirus, especially in immunocompromised patients. It may also be caused by corrosive injury due to caustic ingestions and by pill-induced ulcers.

- **Chamberlain procedure** - anterior parasternal mediastinotomy, a 2-3 cm parasternal incision that allows insertion of a mediastinoscope into the mediastinum or, more commonly, direct visualization and biopsy of mediastinal lymph nodes.
- **Tracheobronchial disruption** occurs usually within 2 cm of the carina.
- **MC chest wall deformity** is pectus excavatum (*funnel chest*)
- **"5-day painful, self curing lesion"** - *thrombosed external hemorrhoid*
- In **malrotation of gut**, **Ladd's bands** course over the horizontal part of the duodenum.
- **Ainhum**: A fissure at the level of **interphalangeal joint of 5th toe**; affects black males; treat by Z plasty.
- Senile angioma = A.k.a **cherry angioma**, **Campbell de Morgan** spots; seen due to skin aging.
- **Lembert sutures**: The classical suture pattern for closing gut/intestines.; **seromuscular sutures**.
- **MC peripheral aneurysms** = **Popliteal Artery Aneurysms**; often bilateral; Second MC is femoral aneurysms.
- **MC aneurysm overall** = **Abdominal Aortic Aneurysms**
- **Incision preferred** for **diaphragmatic surgery** is **circumferential**
- If **large, painful or causing neural deficit**, a **haematoma** may require release by incision or aspiration
- A **drain should be removed as soon as it is no longer required**, as if left in, it can itself predispose to fluid collections as a result of tissue reaction
- **Capacitance coupling** is a phenomenon in laparoscopic surgery which can damage intraabdominal structures - can be prevented by using **entirely plastic ports**.
- **Southampton** wound grading system and **ASEPSIS** wound score is used for grading **severity of wound infections**.
- **Congenital sinuses** = Preauricular, Umbilical, Urachal, Coccygeal, Sacral
- Hidradenitis suppurativa: MC in women, a/w smoking and obesity; presents as tender subcutaneous nodules that may heal with scarring and sinus formation; seen in axilla and groin (apocrine gland areas).
- Suspect **urethral injury** after blunt perineal trauma when the man cannot void, when there is perineal bruising and when there is **blood at the urethral meatus**.
- In the elderly patient with **calcified splenic artery aneurysm**, observation is preferred.
- **5% Dextrose in water (D5W)** is unique in that it may be categorized as both an isotonic and a hypotonic solution.

- **1.5% glycine** is the **MC irrigating solution** used in **TURP**.
- **Suprapubic cystostomy** remains **standard management of prostatic urethral disruption** and straddle injuries to the bulbar urethra
- **MC site of bed sore** (pressure sore or decubitus ulcer) is **Ischium**.
- Common bile duct **T-tubes** should remain in for **10 days**.
- Needle-stick injuries are MC on the **non-dominant index finger** during operative surgery. **Hollow needle injury** carries the greatest risk of HIV transmission.
- **Laparoscopic cholecystectomy** is now the **'gold standard'** for operative treatment of symptomatic gallstone disease.
- **Perforation of the gall bladder** is more common with the **laparoscopic technique** than with the open technique.

FLAIL CHEST

- A flail chest occurs when a segment of the chest wall **does not have bony continuity** with the rest of the thoracic cage.
- This condition usually results from **blunt trauma a/w multiple rib fracture**, i.e. three or more ribs fractured in two or more places; also a/w underlying **pulmonary contusion**.
- Clinical features:
 - On inspiration the loose segment of the chest wall is displaced inwards and less air therefore moves into the lungs (**Paradoxical respiration**).
 - To confirm the diagnosis the chest wall can be observed for paradoxical motion of a chest wall segment for several respiratory cycles and during coughing.
 - Voluntary splinting as a result of pain, mechanically impaired chest wall movement and the associated lung contusion are all causes of the **hypoxia and respiratory failure**
 - The patient is also at high risk of developing a pneumothorax or hemothorax
- **Diagnosis**: is made **clinically**, not by radiography.
- **Treatment**:
 - **Oxygen administration, adequate analgesia** (including opiates) or **epidural analgesia** and **physiotherapy**.
 - **IPPV** (Intermittent positive pressure ventilation) is reserved for cases developing respiratory failure despite adequate analgesia and oxygen
 - **Chest strapping or splinting** should be **avoided**.

Immunohistochemical stains used for tumours

- ▶ Cell type/site of origin:
 - Epithelial (Carcinoma): **cytokeratin**
 - Lymphoid (lymphoma): CD45, CD3, CD20
 - Melanocytic (melanoma): **S100**
 - Neuroendocrine: synaptophysin, chromogranin
 - Vascular: **CD31**
 - Myoid: desmin, actin
- ▶ Site of origin/cell type:
 - Prostate: prostate-specific antigen (PSA)
 - Lung: thyroid transcription factor-1 (TTF-1)
 - Thyroid: thyroglobulin
 - Colorectum: cytokeratin 20 (CK20), CDX2
 - Liver: **HepPar**
 - Gastrointestinal stromal tumour (GIST): CD117, DOG-1
- ▶ Prognosis and treatment:
 - Breast carcinoma: receptors (ER, PR, HER2)
 - Endocrine tumours: **Ki67** proliferative index

Radiological Appearances of pancreatic Conditions

Acute pancreatitis	Chronic pancreatitis	Carcinoma pancreas
<ul style="list-style-type: none"> • Renal halo sign • Gasless abdomen • Ground glass appearance • Colon cut' off sign • Sentinel loop 	<ul style="list-style-type: none"> • Chain of lakes appearance • String of pearl appearance • Beaded appearance • Numerous irregular calcifications are pathognomonic (on X-ray) 	<ul style="list-style-type: none"> • Double contour of medial border of duodenal C loop • Double duct sign • Dilated/widening of duodenal C loop • Mucosal irregularity • Scrambled egg appearance • Inverted/reverse 3 sign of Frostberg • Rose thorning of medial wall of 2nd part of duodenum

Radiological Appearances of Renal Conditions

Radiological features	Seen in	Radiological features	Seen in
ADPKD	Spider leg or Bell deformity Bubble or swiss cheese or sunburst appearance	CA Renal Pelvis	Goblet sign or stipple sign on IVP
Infantile PKD	Sunburst pattern on IVP	Rim/crescent sign	Hydronephrosis
Medullary sponge kidney	Bristles on brush appearance Bouquet of flower appearance	Soap bubble appearance	
Multicystic dysplastic kidney	Bunch of grapes appearance	Spider leg appearance	Polycystic Kidney
Renal artery aneurysm	Ring like calcification	Flower vase appearance	Horse shoe Kidney
Ectopic ureteric orifice	Drooping lily sign on IVP	Golf hole ureter	TB bladder
Retrocaval ureter	Fish hook or reverse 'J' deformity on IVP	Drooping lily sign	Extopic ureter
Retroperitoneal Fibrosis	Medial pulling of ureter or pipestem ureter (Pipestem ureter is also seen in TB)	Cobra head or Adder head appearance	Ureterocele
		Spring onion appearance	
		Egg in cup appearance	Analgesic nephropathy causing papillary necrosis
		Thimble bladder	Tubercular chronic cystitis
		Sandy patches	Schistosomiasis of bladder
		Chalice/Bergman sign	Ureteric dilatation distal to neoplasm
		Fish hook bladder	BPH

Contd...

Contd...

Radiological Appearances of GIT Conditions

Radiological features	Seen in
Wal tail appearance	Achalasia
Apple core lesion on barium enema	Carcinoma colon
Claw appearance on barium enema	In-fussusception
Radiological features	Seen in
Saw tooth appearance	Colonic diverticula
Wid break appearance	Achalasia Volvulus
Cork screw appearance	Diffuse esophageal spasm
Rosary bead appearance	
Pseudodiverticula appearance	
String sign of Kantor	Crohn's disease Tuberculosis
Thumb print sign	Ischemic colitis
Squeeze sign, cushion sign, tenting sign, naked fat sign	Colonic lipoma

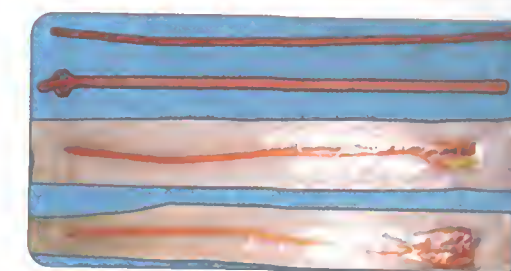


Fig. 22.35: Photo showing red rubber catheter; Malecot's catheter and Foley's catheters



Fig. 22.36: Defibrillator used in case of cardiac arrest



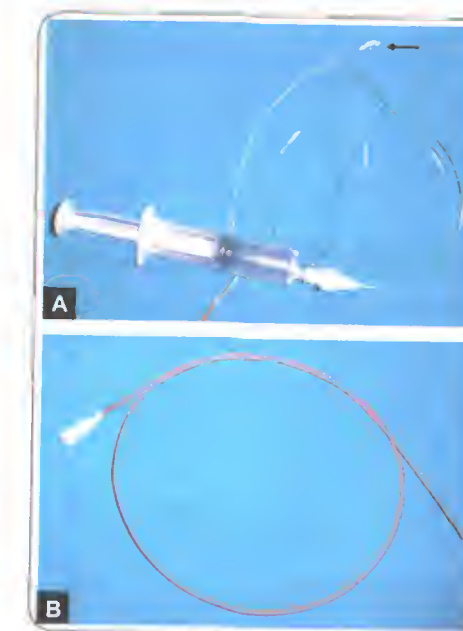
Fig. 22.32: Spinal anaesthesia being given. Note the position of the patient



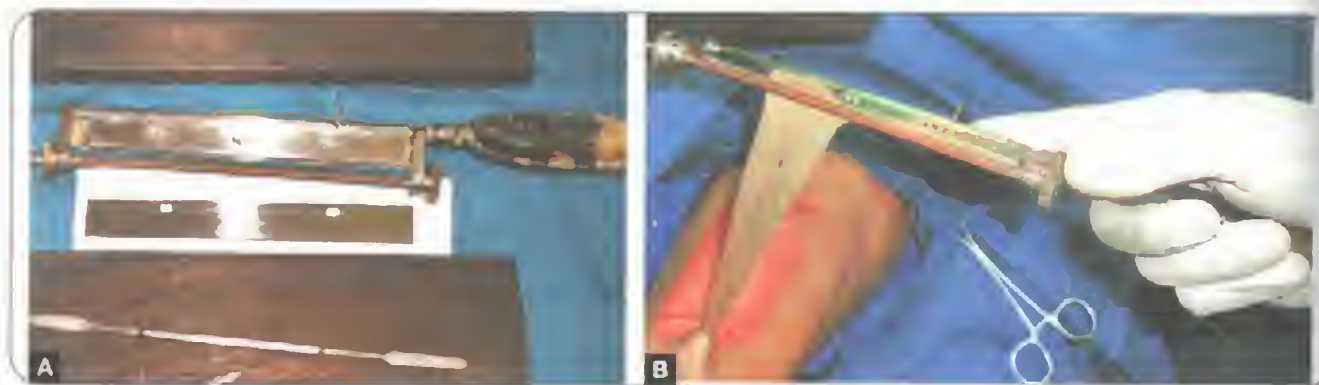
Fig. 22.33: Magill's forceps



Fig. 22.34: Trocar and cannula used for hydrocele surgery



Figs. 22.37A and B: Fogarty's catheter. It is 80 cm in length with 4 to 7 French size. It is used for embolectomy. Note the inflated balloon at the tip



Figs. 22.38A and B: Split skin grafting knife and set; and harvesting

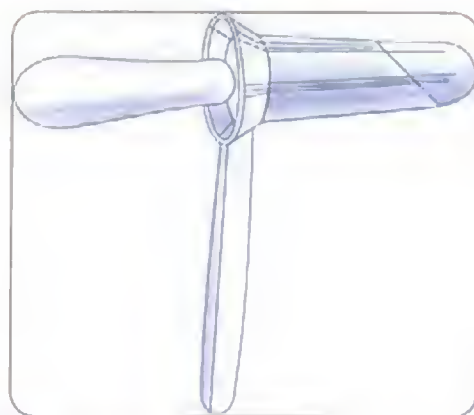


Fig. 22.39: Proctoscope

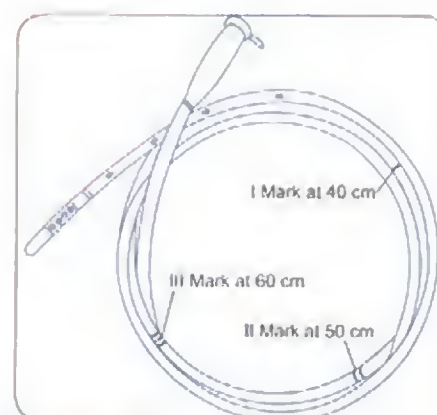


Fig. 22.40: Ryle's tube

CHAPTER

23

Oncology

HIGH YIELD POINTS

- **Neoplasia:** "New Growth".
- **Carcinomas** = "crab-like" infiltrating tumors
- **Sarcomas** = "fleshy tumors".
- **Ame's test** is useful in screening for potential carcinogens, detects *mutagenicity*; this test uses a strain of *Salmonella typhimurium*.
- "Tumor progression" refers to "Sequential appearance of features of increasing malignancy".
- Tumor evolution/progression corresponds to *Darwin's fluxes*

- **Warburg effect:** Even in the presence of ample oxygen, cancer cells demonstrate *aerobic glycolysis* for their metabolism (remember that, normal cells use oxidative phosphorylation in mitochondria under aerobic conditions)
- **Chromothripsis:** "Chromosome shattering"—hundreds of breaks occur within part or across a single chromosome or many chromosomes. This may activate oncogenes and inactivate tumor suppressor genes leading to cancers—seen in *osteosarcomas and gliomas*.

'PLASIA' DEFINITIONS

Reversible

Metaplasia

One adult cell type is replaced by another.

Often 2° to irritation and/ or environmental exposure (e.g. MC is columnar to squamous metaplasia in bronchi of smokers).

Dysplasia

Abnormal growth with loss of cellular orientation and architectural organization.

MC in epithelial cells.

Commonly preneoplastic.

Carcinoma in situ

When *dysplasia* involves the entire thickness of the epithelium, but does NOT penetrate the basement membrane.

Irreversible

Anaplasia

Lack of differentiation is called anaplasia - it is a *hallmark of malignancy*

Desmoplasia

Fibrous tissue formation in response to neoplasm

Neoplasia

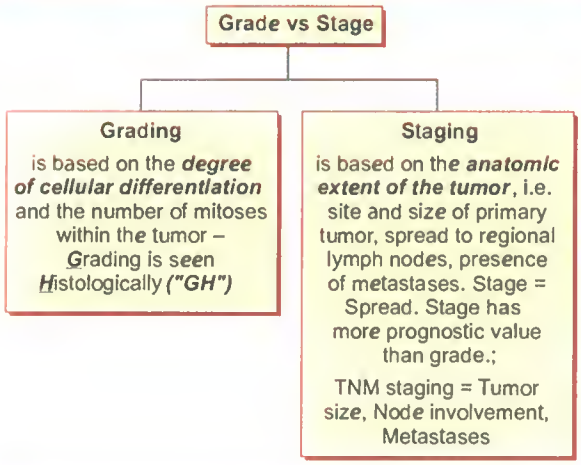
A clonal proliferation of cells that is *uncontrolled and excessive*

EXTRA EDGE

Anaplasia is associated with

- **Pleomorphism** (variation in cell size and shape)
Abnormal nuclear morphology: Nucleus: cytoplasm ratio = 1:1 (normally 1:4 to 1:6)—implies that nucleus is abnormally large.
- **Mitoses:** maximum cells are in mitosis reflecting high proliferation.
- **Loss of polarity** of cells—disorganised growth
- Large central areas of *ischemic necrosis*

TUMOR GRADE VS STAGE



Named Staging/Grading	Organ
Duke staging	Ca colon
Jackson staging	Ca penis
Gleason score	Ca prostate
Robson staging	Renal cell Ca
Nevin staging	Ca Gallbladder
Noguchi classification	Adeno Ca lung
Chang staging	Medulloblastoma
Sullivan modification of Macfarlane system	Adrenocortical Ca
Bloom Richardson grading	Ca Breast
Masaoka staging	Thymomas
Shimida index	Neuroblastoma
Reese Elsworth classification and Esson prognostic index	Retinoblastoma
Bismuth Corlette classification	Perihilar cholangiocarcinoma
Lauren, Ming, Goseki, Borrmann classifications	Gastric Ca

CHORISTOMA VS HAMARTOMA

Choristomas	Hamartomas
Ectopic , sometimes nodular rests of non-transformed tissues (e.g. Pancreatic cells under small bowel mucosa)	Malformations that present as mass of disorganized tissue indigenous to that particular site . (i.e. a hamartomatous nodule in the lung may contain islands of cartilage, bronchi and blood vessels).

Contd...

Contd...

Choristomas	Hamartomas
	<ul style="list-style-type: none">Lung hamartoma: "popcorn" calcificationIris hamartomas: "Lisch nodules" in NeurofibromatosisHamartomatous polyp: Peutz Jeghers syndromeCowden disease: Multiple skin hamartomas + Follicular thyroid Ca

METASTASIS

- Metastasis** is defined by the spread of the tumor to sites that are physically discontinuous from the primary tumor
- Most reliable** feature of malignancy is **metastases**; **second** most reliable feature is **invasiveness**.
- Lymphatic spread** is the **MC pathway** for metastases.
- A **sentinel node** is the first node in the regional lymphatic basin that received lymph flow from the primary tumor.
- Hematogenous** spread is typical of **sarcomas**.
- Metastatic tumors (secondaries) of liver, bone, brain are **more common than their respective primary tumors**.
- Lung** is the **MC site of metastatic** neoplasms.

PATHWAYS OF SPREAD OF CANCER

- Lymphatic Spread**: **MC** pathway for dissemination of **carcinomas**; sarcomas may also use this route. (ALSO, **overall MC method** of spread of cancers since carcinomas are MC than sarcomas!).
 - Sentinel lymph node** is defined as 'the first node in a regional lymphatic basin that received lymph from the primary tumor.'
 - A sentinel lymph node biopsy (**SLNB**) is a procedure in which the sentinel lymph node is identified, removed, and examined to determine whether cancer cells are present.
 - SLNB is commonly done in **Ca breast and melanomas**
 - The concept of SLNB was **first** introduced in **Ca penis** by **Cabana**.
- Hematogenous spread**: Typical of sarcomas, but may also be seen with carcinomas.
 - Common organs involved in hematogenous spread are **lungs** (since all caval blood flows here) and **liver** (since all portal area drainage flows to the liver).
 - Cancers arising in **proximity to vertebral column (thyroid and prostate)** often embolise through paravertebral plexus of veins.

Contd...

- Cancers with propensity for **venous invasion**: **Renal cell Ca; Hepatocellular Ca; Follicular Ca thyroid**.
- Seeding of body cavities** and surfaces: **MC the peritoneal cavity** is involved. Especially with **ovarian** neoplasms.
 - Pseudomyxoma peritonei**: Mucus secreting appendiceal and ovarian carcinomas fill the peritoneal cavity with a gelatinous mass.
- Iatrogenic spread** of surgical instruments: Very **rare**; hence **FNAC or biopsy of testicular tumors** is NEVER done.

Types of metastases:

- Skip metastases**:
 - Bypassing of local lymph nodes with involvement of more distant lymph nodes; Also a tumor nodule that is located within the same bone as the main tumor BUT not in continuity with it.
 - Examples are: Ca **lung**, **Osteosarcoma**, Ca **esophagus**; papillary Ca thyroid, **Oral** Ca, Breast Ca (rarely).
- Retrograde metastases**:
 - Due to obstruction of lymphatics by tumor cells, the lymph flow is disturbed and tumor cells spread against the flow of lymph causing retrograde metastases at unusual sites. Examples are:
 - Metastases of Ca prostate to supraclavicular N
 - Metastases of Ca adrenals to lung
 - Metastases of Ca lung to axillary lymph nodes
- Drop metastases**:
 - Intradural but extramedullary spinal metastases that arise from intracranial lesions are called drop metastases (MC in **children**). Examples are:
 - Medulloblastoma** (MC 50%)
 - Glioblastoma
 - Ependymoma
 - Germinoma
 - Pinealoblastoma
 - Astrocytoma

EXTRA EDGE

- Cancers which **rarely metastasize**: Glioma of CNS, BCC of skin
- Pulsating metastases** seen in bone secondaries from RCC usually (rarely from thyroid Ca).

Common Sites of Primary Tumors

Organ with metastases	MC site of primary
Liver	Colon Ca
Bone	Prostate (in males) Breast (in females)

Contd...

Organ with metastases	MC site of primary
Brain	Lung Ca
Leptomeningeal metastases	Breast Ca
Orbit	In adults (Ca breast) In children (Neuroblastoma)
Testis	Prostate

ONCOGENES

- Proto-oncogenes** are a group of genes that cause normal cells to become cancerous when they are mutated.
- Mutations in proto-oncogenes are typically dominant in nature, and the **mutated version of a proto-oncogene** is called an **oncogene**.
- Proto-oncogenes** encode proteins that function to **stimulate cell division, inhibit cell differentiation, and halt cell death**—all of these processes are important for **normal human development** and for the **maintenance of tissues and organs**.
- Oncogenes**, however, typically exhibit increased production of these proteins, thus leading to **increased cell division, decreased cell differentiation, and inhibition of cell death**—all these phenotypes typically **define cancer cells**.
- When a proto-oncogene mutates (changes) into an oncogene, it becomes **permanently "turned on" or activated** when it is not supposed to be.
- Thus, oncogenes are currently a major molecular target for anti-cancer drug design.

Oncogenes and Associated Cancers

Oncogene	Associated Cancer
Growth Factors	
PDGFB	Astrocytoma
TGFA	Astrocytoma
HGF	Hepatocellular carcinoma Thyroid cancer
HST1	Osteosarcoma
FGF3	Stomach, Bladder, Breast, Melanoma
INT2	Breast
KS3	Kaposi sarcoma
Growth Factor Receptors	
Erb B1 (EGFR)	Adeno Ca Lung
Erb B2 (HER)	Breast
FLT3	Leukemia
RET	MEN 2A and 2B Familial medullary thyroid Ca

Contd...

Contd...

Oncogene	Associated Cancer
PDGFRB	Gliomas, Leukemias
KIT	GIST, Seminoma, Leukemia
ALK	Adeno Ca Lung
TRK	Colon, Thyroid
MAS	Epidermoid Ca
Proteins involved in signal transduction	
ABL	Chronic Myeloid Leukemia (CML) Acute Lymphoblastic Leukemia (ALL)
BRAF	Melanoma, Colon, Thyroid, Leukemia
JAK2	Myeloproliferative disorders ALL
NOTCH1	Leukemia, Lymphoma, Breast Ca
KRAS	Colon, Lung, Pancreas
HRAS	Bladder and Kidney tumors
GNAQ	Uveal melanoma, Sturge Weber syndrome
GNAS	Pituitary adenoma
Nuclear Regulatory proteins	
cMYC	Burkitt's lymphoma
<u>N</u> -MYC	<u>N</u> euoblastoma
<u>L</u> -MYC	Lung Ca
Cell Cycle Regulators	
CCND1 (Cyclin D1)	Mantle cell lymphoma, multiple myeloma, Breast, Esophageal
CDK4	Glioblastoma, melanoma, sarcoma

TUMOR SUPPRESSOR GENES

- **Tumor suppressor genes** are normal genes that slow down cell division, repair DNA mistakes, and tell cells when to die (*apoptosis*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

Tumor suppressor gene	Associated cancer
Rb1	Retinoblastoma
p53	Li-Fraumeni syn. (leukemias, brain tumors, sarcomas) p53 is " guardian of the genome/G1 checkpoint ".
WT1	Wilms tumor

Contd...

Contd...

Tumor suppressor gene	Associated cancer
BRCA-1, BRCA-2	Familial BR east cancer
NF-1	Neurofibromatosis-1 (protein = neurofibromin 1)
NF-2	Neurofibromatosis-2 (protein = merlin, neurofibromin 2)
VHL	<i>Von Hippel-Lindau syn.</i> (renal Ca, hemangioblastomas, pheochromocytoma, retinal angioma)
INK4a	Melanoma (<i>melanoma and ink are both dark!!</i>)
DCC	Colon cancer (DCC = deleted in colorectal carcinoma)
APC	Colon cancer (with polyposis); APC = Adenomatous polyposis coli
MLH1, MSH2, MSH6	Colon cancer (without polyposis)
DPC	Pancreatic cancer (DPC = Deleted in Pancreatic Cancer)
PTCH	Gorlin syndrome
PTEN	Cowden syndrome
SMAD2, SMAD4	Juvenile polyposis
CDKN2A	Familial melanoma
STK11	Peutz Jegher's syndrome
CDH1	Familial gastric cancer

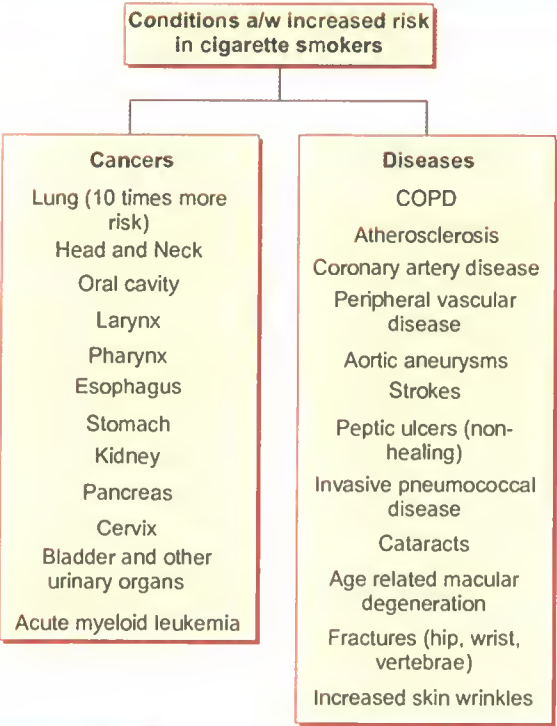
FAMILIAL MALIGNANCIES/CANCERS

- Although the majority of cancers are sporadic (90–95%) there may be several cases of sporadic cancers within one family, possibly due to shared environments, shared lifestyles, or weak genetic factors (low-risk genes) familial cancer therefore, does not necessarily imply the presence of a dominant predisposing gene.
 - 'Family history' may be present in upto 20% of cases e.g. breast cancer
 - 'Family history of cancer' does not confirm hereditary susceptibility
 - 'Familial cancer' does not mean hereditary cancer
 - 'Familial cancer' can be due to one or more of the following
 - ★ Shared environmental factors
 - ★ Chance, since the disease is common
 - ★ Shared genetic factors which may be: many different 'weak' genes (polygenic susceptibility); strong predisposing genes (dominant susceptibility).

Examples of Familial Malignancies

Disorder	Tumor/cancer	Remarks
Chromosomal syndromes		
Chromosome 11p-WT1 gene	Wilms tumor	Aniridia, Genitourinary anomalies, mental Retardation (WAGR)
Chromosome 13q- RB1 gene; Knuton's two-hit hypothesis	Retinoblastoma, osteosarcoma	Associated metal retardation, skeletal malformation, AD or sporadic new mutation
Trisomy 21 (Down's)	Lymphocytic or nonlymphocytic leukemia	Risk is 15 times normal
Klinefelter's syn. (47 XXY)	Breast cancer, extragonadal germ cell tumors	
Gonadal dysgenesis (XO/XY)	Gonadoblastoma	Gonads must be removed; 25% chance of gonadal malignancy
DNA fragility		
Xeroderma pigmentosum	Basal, squamous cell skin cancers	AR, failure to repair solar damaged DNA
Fanconi's anemia	Leukemia, AML	AR; positive diepoxybutane test; chromosome fragility
Bloom's syn.	Leukemia, lymphoma	AR; chromosome fragility
Ataxia-telangiectasia	Lymphoma, leukemia	AR; sensitive to X-rays, radiomimetic drugs; chromosome fragility
Dysplastic nevus syn.	Melanoma	AD
Immunodeficiency syndromes		
Wiskott-Aldrich syn.	Lymphoma, leukemia	XLR , Immunodeficiency,
X-linked Immunodeficiency	Lymphoma(Duncan's syn.)	EBV
X-linked agammaglobulinemia	Lymphoma, leukemia	Immunodeficiency
Sever combined immunodeficiency (SCID)	Lymphoma, leukemia	Adenosine deaminaze (ADA) deficiency
Others		
Tuberous sclerosis	Fibroangiomatous nevi, myocardial rhabdomyoma	AD
Hemochromatosis	Hepatoma	Cirrhosis, AD/AR
Gardner syn.	Adenocarcinoma of colon, skull and soft tissue tumors	AD, APC gene
Peutz-Jeghers syn.	GI carcinoma, ovarian neoplasia	AD
Tyrosinemia, galactosemia	Hepatic carcinoma	Nodular cirrhosis, AR
MEN 1 (Wermer's syn.)	Parathyroid adenoma, Pancreatic islet cell tumor, Pituitary adenoma, carcinoid	AD, Zollinger-Ellison syn. PPP
MEN 2A (Sipple syn.)	Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism	AD, monitor calcitonin and calcium levels
MEN 2B (MEN 3)	Medullary thyroid carcinoma, pheochromocytoma, Mucosal neuroma, Marfanoid habitus,	

CIGARETTE SMOKING



EXTRA EDGE

- Smoking cessation drugs:
 - Bupropion (antidepressant—acts by boosting brain levels of dopamine and norepinephrine);
 - Varenicline, a partial nicotinic acetylcholine-receptor agonist; nicotine patch, gum and lozenges

SUSPECTED CARCINOGENS

Etiology	Cancer
Physical agents	
Ionizing radiation	Leukemia, thyroid, breast
Ultraviolet radiation	Melanoma, basal and squamous cell carcinoma in xeroderma pigmentosum
Chemical agents	
Diethylstilbestrol (prenatal)	Vaginal clear cell Ca in daughter
Asbestos	Mesothelioma
Androgens, Aflatoxin	Hepatocellular carcinoma
Vinyl chloride	Hepatic angiosarcoma
Alcohol (fetal alcohol syndrome), prenatal phenytoin	Neuroblastoma

Contd...

Contd...

Etiology	Cancer
Cyclophosphamide	Bladder cancer, leukemia
Aniline dyes and Aromatic dyes	Bladder cancer
Intramuscular iron	Sarcoma at injection site
Pesticides	Possible leukemia, brain tumors
Phytoestrogens	Reduced risk for breast cancer
Benzene	AML, myelodysplasia
Chloramphenicol, Alkylating agents, Topoisomerase II inhibitors	AML
Immunosuppressant drugs, Phenytoin	Lymphoma
Chromium	Lung Ca
Radon gas	Lung Ca
Microbiologic agents	
Helicobacter pylori	Gastric Ca, MALT lymphoma
Hepatitis B, C viruses	Hepatic carcinoma
Human immunodeficiency virus (HIV)	Leiomyosarcoma
Schistosoma haematobium	Bladder carcinoma
Clonorchis sinensis	Biliary tract cancer
Epstein-Barr virus	African Burkitt's lymphoma, nasopharyngeal carcinoma, post-transplant lymphoma
Human Herpes virus 8 (HHV8)	Kaposi's sarcoma
Human Papilloma virus (HPV)	Cervical cancer, Anal SCC, Ca oropharynx
Human T lymphotropic virus I	T-cell lymphoma
Simian virus 40	Possible ependymoma, choroid plexus tumor, osteosarcoma, mesothelioma

EXTRA EDGE

- Some chronic inflammatory states that may lead to cancers are
 - Lichen sclerosis: Vulvar squamous cell cancer
 - Sjogren syndrome, Hashimoto's thyroiditis: MALT lymphoma
 - Chronic cystitis (schistosomiasis): Ca bladder
 - Opisthorchis cholangitis: Cholangiocarcinoma, Colon Ca

TUMOR MARKERS

Tumor marker	Cancer
Hormones	
Human chorionic gonadotropin (HCG)	Gestational trophoblastic disease, Gonadal germ cell tumor
Calcitonin	Medullary thyroid Ca
Catecholamines (Epinephrine, norepinephrine)	Pheochromocytoma
Oncofetal antigens	
Alphafetoprotein (AFP)	Hepatocellular Ca, gonadal germ cell Tumor (NOT pure seminoma)
Carcinoembryonic antigen (CEA)	Colon cancer Others- pancreas, lung, breast, ovary
Enzymes	
Neuron-specific enolase	Small cell Ca of the lung, neuroblastoma
Prostatic acid phosphatase	Ca Prostate
Lactate dehydrogenase	Lymphoma, Ewing's sarcoma
Alkaline phosphatase	Osteosarcoma
Placental alkaline phosphatase	Ca ovary, seminoma
Tumor associated proteins	
Prostate specific antigen (PSA)	Prostate cancer
Monoclonal immunoglobulin	Multiple Myeloma
Bladder tumor antigen (BTA)	Bladder cancer
CA 15-3	Breast cancer
CA 27.29	Breast
CA 125 (a glycoprotein)	Ovarian cancer Other cancers - breast, hepatoma, lymphomas
CA 19-9 (a carbohydrate)	Pancreatic, colon, cancer
CD30	Hodgkin's disease, anaplastic large cell lymphoma
CD25	Hairy cell leukemia, adult T-cell leukemia/lymphoma
CD100	Melanoma, CNS and nerve tumors

Contd...

Contd...

Tumor marker	Cancer
Intermediate filaments	
Keratins	Carcinomas, mesotheliomas
Desmin	Muscle tumors
Vimentin	Sarcomas
Others	
Factor VIII	Kaposi's sarcoma, angiosarcoma
Serum ferritin	Hepatoma
Thyroglobulin	Thyroid cancer and thyroid disorders

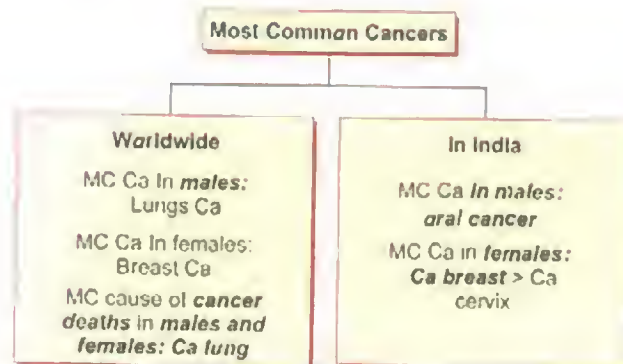
HUMAN ONCOGENIC VIRUSES

Virus	Associated cancers
DNA viruses	
Human Papilloma virus (HPV)	Genital (cervical, vulvar, penile) warts may progress to carcinoma
Epstein Barr virus (EBV)	Gastric cancer (MC EBV associated cancer); Anaplastic nasopharyngeal carcinoma; Burkitt's lymphoma (African type); Hodgkin's lymphoma (Mixed cellularity type); CNS lymphoma in AIDS patients
Human Herpes Virus 8 (HHV 8)	Kaposi's sarcoma
Hepatitis B virus (HBV)	Primary hepatocellular carcinoma
RNA viruses	
Human T cell leukemia virus (HTLV1)	T cell leukemia/lymphoma
Hepatitis C virus (HCV)	Primary hepatocellular carcinoma

COMMON CANCERS BY GEOGRAPHICAL LOCATIONS

- India
 - Oral cancer
- Japan
 - AdenoCa Stomach
- South East Asia
 - Nasopharyngeal Ca, Hepatocellular Ca.

- **Africa** Burkitt's lymphoma
- **Sub-Saharan Africa** Hepatocellular Ca
- **South Africa (Bantus)** Thyroid Ca



MC childhood tumors

- MC pediatric malignancy overall: Leukemia (ALL is MC)
- MC brain tumor in children: **Pilocytic astrocytoma** (a type of glioma)
- MC primary malignant brain tumor of childhood: **Medulloblastoma**
- MC intraocular tumor in children: **retinoblastoma**
- MC renal tumor in children: **Wilm's tumor**
- MC soft tissue tumor in children: **rhabdomyosarcoma**

Hormone Dependent Tumors

- **Estrogen:** Endometrial Ca

pain, bronchial obstruction, wheezing, pneumonic 'coin' lesions on x-ray film.

- Major source of **hemoptysis** are **bronchial arteries**
- Small cell: Non-small cell Ca (MC) = 1:4.
- MC site of **metastases** is **adrenals**.
- Integrated **PET-CT scan** is the **best imaging modality** for diagnosis and staging.

Type	Characteristics
Squamous cell Ca	<ul style="list-style-type: none"> • Central location • MC lung cancer in Cigarette smokers • MC histologic type in India • MC Lung Ca detected by positive sputum Cytology; <i>More likely to cause hemoptysis</i> • MC Lung Ca leading to Pancoast tumor • Hilar-mass arising from branchial epithelium, Cavitation; direct extension to hilar lymph nodes • PN: Parathyroid like activity (PTHrP) – hyperCalcemia; dermatomyositis • Histology: Keratin pearls and intercellular bridges • Best prognosis • Treatment: surgery • On IHC: Stain for P63 and P40.

- **TSH:** Papillary Ca thyroid
- **Androgen** dependant: Prostate Ca
- **Progesterone** dependant: Breast Ca
- Renal cell Ca
- Follicular Ca thyroid
- Hepatocellular carcinoma

Tissue Resistant to Tumor Invasion

- Mature cartilage
- Elastic tissue of artery

Primary prevention modalities of cancer

- **Aspirin:** ↓ risk of esophageal, stomach, colorectal Ca.
- **Isotretinoin, Vit E, Se:** ↓ leukoplakia in lungs and GIT
- **Tamoxifen:** ↓ risk of second primary malignancy in spared breast, also ↓ incidence in women who have strong family history
- **Calcium:** ↓ risk of colon Ca

LUNG CANCER

- Lung cancer is the **leading cause of cancer deaths** in both men and women.
- Risk factors:
 - Tobacco/**smoking** (> 10 fold risk)
 - Air pollution (**Radon**)
 - Exposure to **asbestos, uranium and nickel**.
 - **Old infarcts** and **lungs scars** (most progress to **adenoCa**)
 - Ionizing radiation exposure
- Presents with **cough (MC)**, hemoptysis, dyspnea, chest

Contd...

Contd...

Type	Characteristics
Adeno Ca	<ul style="list-style-type: none"> • Peripheral, arises from mucus glands; maybe a/w EGFR mutations (better prognosis) • MC histologic type • MC lung cancer in non-smokers and females • Develops in site of prior pulmonary inflammation or injury • Wide metastases, a/w asbestosis; pleural effusions show ↑ hyaluronidase levels. • 2 types are bronchial and (bronchioloalveolar—also called adenoCa in situ) • Histology: Clara cells, type 2 pneumocytes • PN: DIC, thrombophlebitis, microangiopathic hemolytic anemia • Good prognosis • Noguchi classification is used • On IHC: Stain for TTF-1 (Thyroid Transcription factor-1) and Napsin-A.
Small cell (oat cell) Ca	<ul style="list-style-type: none"> • Central; infiltrated submucosally and causes bronchial lumen obstruction. • Rapidly growing, early distant hematogenous metastases; aggressive course • PN: SIADH, Ectopic GH and ACTH secretion, peripheral neuropathy, Eaton Lambert syndrome • MC lung Ca causing SVC syndrome • Neoplasm of neuroendocrine Kulchitsky cells – Small blue round cell tumor • Azzopardi effect: Blood vessels in necrotic area may show smudged hematoxyphilic material in their walls, which represents DNA released from Tumor cells. • Excellent response to chemotherapy (cisplatin and etoposide) • >90% cases are a/w chromosome 3p deletion.
Large cell Ca	<ul style="list-style-type: none"> • Least common type of lung Ca and least common type of NSCLC also • Peripheral • Highly undifferentiated anaplastic tumor, rapid doubling time, aggressive clinical course—Poor prognosis • Less tendency to metastasize • PN: Gynecomastia • Less responsive to chemotherapy • Treat surgically

PN = Paraneoplastic syndrome; SVC = Superior Vena Cava; SIADH = Syndrome of Inappropriate secretion of ADH; DIC = Disseminated Intravascular Coagulation.

1. **Pancoast tumor:** Carcinoma that occurs in the apex of the lung and may affect cervical sympathetic plexus causing Horner's syndrome
2. **SVC syndrome:** Swelling of face and arm, MC on the right side and elevated JVP; treated with radiotherapy.
3. **Trousseau's syndrome:** A hypercoagulable state seen MC with adenocarcinoma.
4. **Eaton-Lambert syndrome:** Autoantibodies against calcium channels, clinically similar to myasthenia, except that muscle **fatigue improves with repeated stimulation**.
5. **For treatment and prognosis purposes:** Classified as SCLC (small cell lung cancer) and NSCLC (Non SCLC).

Drugs for Chemotherapy of Lung Ca

- For SCLC:

- **Cisplatin/Carboplatin + etoposide/irinotecan;** excellent response—following chemoradiation) chemotherapy with concurrent thoracic radiotherapy).
- **Prophylactic cranial irradiation** is given to prevent CNS recurrence and improve survival in SCLC patients.
- For NSCLC (mainly for stage IV tumors):
 - If +ve EGFR mutations—**EGFR inhibitor (erlotinib, gefitinib or afatinib)** is used.
 - If +ve **EMLA-ALK**-mutations: (**adenocarcinoma, nonsmoking, Asians**)—**crizotinib** is used.
 - ★ If +ve, **T790M mutation** = **Osimertinib** is used.
 - If no mutation/mutation for which there is no approved FDA therapy: **platinum doublet** (cisplatin or carboplatin + gemcitabine, taxane, vinorelbine, or pemetrexed) + **bevacizumab** (Anti-VEGF).

Surgery for Lung Ca

- For SCLC:

- Surgical resection is NOT routinely recommended for patients because even patients with Limited Disease (LD) SCLC still have occult micrometastases.
- **For NSCLC:**
 - **Surgery** is the **treatment of choice** for NSCLC Tumors staged **upto T3N1M0 (includes stage I, II)**.
 - **Stage III—Combined modality** approach.
 - **Stage IV—Medical Rx only** - palliative chemotherapy as in drugs mentioned above.

TNM Staging of Lung Cancer

T stage

- T0:** No evidence of primary tumor
- T1:** Tumor ≤3 cm, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion, more proximal than the lobar bronchus
- T1a:** Tumor ≤2 cm; **T1b:** Tumor >2, but ≤3 cm
- T2:** Tumor >3, but ≤7 cm or Tumor with any of the following: Invades visceral pleura, involves main bronchus ≥2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum, but not involving the entire lung
- T2a:** Tumor >3, but ≤5 cm; **T2b:** Tumor >5, but ≤7 cma
- T3:** Tumor >7 cm or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; or Tumor in the main bronchus <2 cm distal to the carina; or atelectasis/obstructive pneumonitis of entire lung; or separate Tumor nodules in the same lobe
- T4:** Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body or carina, or separate Tumor nodules in a different ipsilateral lobe

N stage

- N0:** No demonstrable metastasis or regional lymph node
- N1:** Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension
- N2:** Metastasis to the ipsilateral, mediastinal and subcarinal lymph nodes
- N3:** Metastasis to the contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes

M stage

- M0:** No known distant metastasis
- M1a:** Separate Tumor nodules in a contralateral lobe, or Tumor with pleural nodules or malignant pleural dissemination
- M1b:** Distant metastasis

Malignant Mesothelioma

- A/w **BAP-1** tumor suppressor gene mutation.
- **MC tumor** of the **pleura**
- **MC** in **males > 40 years age**.

- A/w exposure to **asbestos** (particularly the *crocidolite* form); latent period =20-40 years.
- Types:
 - **Epithelioid** (MC and best prognosis);
 - **Sarcomatoid** (worst prognosis)
 - **Biphasic** - mixture of above 2 types
- **NO** association between smoking and mesothelioma.
- **Unilateral, nonpleuritic chest pain and dyspnea.**
- **Pleural effusion (hemorrhagic)** or pleural thickening or both on chest radiographs.
- **Malignant cells** in pleural fluid or tissue biopsy, Progresses rapidly.
- **Chemotherapy is mainstay** of treatment; surgery, radiotherapy, and a combination of methods has been attempted.
- Note: Primary abdominal (**peritoneal**) malignant **mesothelioma (20%)** is rare; a/w **hemorrhagic ascites**.

BENIGN LIVER TUMORS

Hepatic adenoma

- A.k.a hepatocellular adenoma
- **MC in women;** of child bearing age; may be related to **OCP intake;**
- Usually **solitary**, occur MC in the **right lobe** of the liver
- **Well circumscribed** and **vascular solid tumor.**
- Pathology: Sheets of hepatocytes **without bile ducts** or **portal areas**. Increased **glycogen** and **fat present**. **Kupffer cells, if present, are reduced** in number and are nonfunctional.
- Can cause **acute abdominal pain** due to **necrosis of the Tumor with hemorrhage;**
- **Tc99m liver scan reveals a cold defect** (because phagocytizing **Kupffer cells are absent**);
- Risk of **malignant change** is about **10%.**
- **Elective surgical resection** is treatment of choice all lesions greater than 5 cm in diameter

Focal Nodular Hyperplasia

- **MC in women;** **haemorrhage and necrosis are rare,** NOT a/w OCPs;
- Often asymptomatic and hypervascular on CT scan or MRI;
- Tc99m liver scan shows **hot spot** due to presence of liver cells.
- Hepatocytes, bile ductules and Kupffer cells **ARE** present.
- **Sulfur colloid scan** of liver helps in diagnosis
- Treatment by observation only.

- FNHs exhibit a characteristic **central scar** that is hypovascular on the arterial- phase and hypervascular on the delayed-phase CT images.

Hemangioma

- **MC benign liver tumor;** **cavernous** type.
- Often an **incidental** finding on CT scan.
- **Giant hemangiomas** require **excision**, otherwise observation only.
- Percutaneous **biopsy** should be **avoided**.

MALIGNANT LIVER TUMORS

1. Hepatocellular Carcinoma (HCC)/Hepatoma

- Arises from **liver parenchymal cells**.
- Especially prevalent in areas of **sub-Saharan Africa** and **Asia**; **MC in men**; peaks in the fifth to sixth decade of life in western countries but arises **one to two decades earlier in Asia and Africa**.

Risk Factors for HCC

Common	Uncommon
<ul style="list-style-type: none">• Chronic hepatitis B (100 fold increased risk) and hepatitis C• Cirrhosis (from any cause),• Chronic Alcohol,• Hemochromatosis• Aflatoxin B1• Nonalcoholic fatty liver; Nonalcoholic steatohepatitis.	<ul style="list-style-type: none">• Exposure to long term estrogens in the form of contraceptives or androgens• Alpha-1-antitrypsin deficiency• Tyrosinemia,• Citrullinemia• Porphyria, cutanea, tarda,• Wilson's disease

- **Presentation: Abdominal pain** (**MC symptom**), **hepatomegaly** (**MC sign**), right upper quadrant mass, friction rub or bruit over the liver (**25% cases**), blood tinged ascites (in **20% cases**), jaundice is **RARE**
- Tumor markers elevated:
 - **Alpha fetoprotein (AFP)** esp, **AFP-L3** (elevated in **70% patients**)
 - **Des-γ - carboxy prothrombin**, a Protein Induced by Vitamin K Absence (PIVKA-2)
 - **Glypican-3**
 - **Serum Alkaline phosphatase** is also elevated.
- **Liver biopsy** is diagnostic.
- On CT and MRI: Arterial phase enhancement of the lesion followed by **delayed hypointensity** ("**washout**") is **most specific** for HCC.
- HCC has propensity to **invade portal vein**.

Staging systems for HCC

- **AJCC TNM** (American Joint Committee on cancer)
- **CLIP** (Cancer of the Liver Italian program)—(Includes Portal vein thrombosis, AFP, Child pugh score, Tumor extent - "**PACT**")
- **Okuda** staging (includes Bilirubin, Albumin, Tumor Extent, Ascites - "**BATA**")
- **BCLC** (Barcelona Clinic Liver Cancer)
- **CUPI** (Chinese University Prognostic Index)
- **JIS** (Japanese Integrates Staging Score)
- **SLiDe** (Stage, Liver damage, Des γ - carboxy prothrombin)

Treatment

- For patients without cirrhosis who develop HCC, **resection** is treatment of choice.
- For those with Child's class A cirrhosis with preserved liver function and no portal HTN, resection is also considered.
- If **resection is not possible** because of poor liver function and the **HCC meets the Milan criteria**, **liver transplantation** is treatment of choice.
- **Milan criteria** = (1) one nodule < 5 cm (2) three nodules all < 3 cm (3) no gross vascular invasion or extrahepatic spread.
- For unresectable HCC: **Sorafenib**, an oral **multikinase inhibitor** of **Rafkinase** and **VEGF**.

Treatment Options for HCC

Surgical	Trans-arterial (through hepatic artery)
<ul style="list-style-type: none">• Resection• Ortho optic Liver Transplantation	<ul style="list-style-type: none">• Embolization• ChemoEmbolization (TACE)• ChemoInfusion (TACI)• RadioEmbolisation (TARE)• Radiotherapy (Yttrium 90 (pure beta emitter) and Iodine 131-Ethiodol)
Ablative	Systemic
<ul style="list-style-type: none">• Ethanol injection• Acetic acid injection• Thermal ablation (radiofrequency, cryotherapy, microwave)	<ul style="list-style-type: none">• Chemotherapy• Hormonal• Immunotherapy
Combined trans-arterial and ablative	EBRT (External Beam Radiotherapy)

Fibrolamellar variant of hepatocellular carcinoma

- Typically a disease of **younger women** (F > M; as per H-19th/552)
- AFP negative, Normal LFTs**; NO cirrhosis; NO HBV association; ↑ Blood neurotensin
- Adult-type portal vein invasion is less common.
- Metastases are common, especially to lungs and local regional lymph nodes
- Surgical resection is treatment of choice; Better Survival than with adult-type HCC.**

2. Hepatoblastoma

- A tumor of **infancy** that typically is *a/w very high serum AFP levels*;
- Lesions are usually solitary, may be respectable, and have a better prognosis than HCC.

3. Angiosarcoma

- It consists of *vascular spaces lined by malignant endothelial cells*
- A/w exposure to polyvinyl chloride, arsenic and androgenic anabolic steroids.*

4. Metastases to Liver

- Predominantly from **colon, pancreas, and breast carcinomas**
- Ocular melanomas** are prone to liver metastasis.
- Gall Bladder Ca also causes **multiple secondaries** in liver
- Synchronous liver metastases** (liver metastases detected at the time of initial diagnosis of the primary cancer—e.x. colon cancer) are *a/w poor prognosis*
- Metastases from **Breast ca** are **HYPOechoic** on ultrasound and mets from **mucinous adenocarcinoma** of colon are **calcified**.

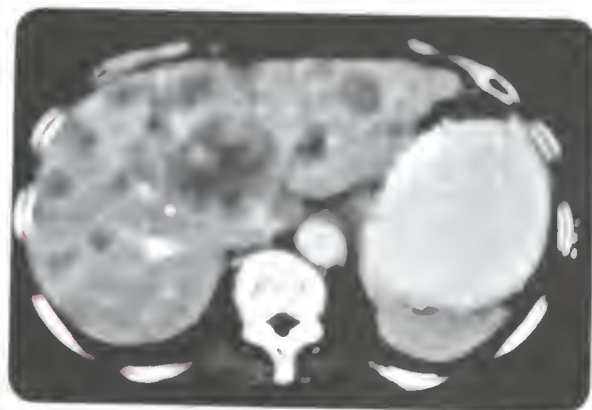


Fig. 23.1: Secondaries in liver. Note the multiple lesions (nodules) in both lobes of the liver

CANCER OF THE GALLBLADDER

- Risk factors:**
 - Gallstones**
 - Chronic infection of the gallbladder with **Salmonella typhi**
 - Gall bladder polyps** over 1 cm in diameter,
 - porcelain gallbladder**, and
 - Anomalous pancreaticobiliary ductal junction**;
 - K-ras and TP53 mutations.
- F: M = 4: 1**; mean age at diagnosis is about **70 years**
- 90% are **adenocarcinomas**; MC **scirrhous carcinoma**
- Similar presentation to benign disease—i.e. gallstones
- Painless obstructive jaundice with palpable mass** in the right hypochondrium (gallbladder)—signifies malignant disease (**Courvoisier's law**).
- Most patients present with **advanced disease** and prognosis is **poor—approx, 6 months.** (worse than bile duct Ca)

CHOLANGIOCARCINOMA

- Bile duct Ca that develops from the intra or extrahepatic biliary tree; usually an adenocarcinoma

Risk Factors for Cholangiocarcinoma

- Chronic inflammatory conditions: Primary sclerosing **cholangitis**; Oriental **cholangiohepatitis**; **Hepatitis C** infection; chronic ulcerative colitis
- Parasitic infestations: *Clonorchis sinensis*, *Fasciola hepatica*, *Opisthotic viverrini*
- Congenital: **Choledochal** cyst, **Caroli's** disease
- Chemicals: **Thorium** dioxide; **Dioxin**, **Vinyl chloride**, **Asbestos**
- Post-surgical: Biliary enteric anastomosis
- MC site is at the **common hepatic duct bifurcation** (**perihilar** or **Klatskin tumors**).
- Over 90% of tumors present with **obstructive jaundice**
- Prognosis is **poor**.

Treatment of above 2 biliary tumors

- In young and fit patients, curative surgery may be attempted if the tumor is well localized.
- Rest of patients—radiotherapy, chemotherapy, palliative care.

Bismuth-Corlette classification for perihilar cholangiocarcinoma

- Type I:** Limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts
- Type II:** Involves the **confluence** of the right and left hepatic ducts

- Type IIIa:** Type II and extends to the bifurcation of the **right hepatic** duct
- Type IIIb:** Type II and extends to the bifurcation of the **left hepatic** duct
- Type IV:** Extending to the bifurcations of **both** right and left hepatic ducts or multifocal involvement
- Type V:** Stricture at the junction of common bile duct and cystic duct

PANCREATIC CANCER

Risk factors for pancreatic cancer:

- Cigarette/tobacco**; **alcohol** use; **obesity**; chronic pancreatitis, prior abdominal **radiation**, diabetes mellitus, **black males**.
- Genetic: **K-ras mutations**; tumor suppressor gene inactivations (**p53**, **p16**, **INK4A**, **SMAD4**); **survivin** is overexpressed.
- Hereditary syndromes:** Hereditary pancreatitis, familial atypical multiple mole melanoma (FAMMM), Peutz-Jeghers syndrome, ataxia-telangiectasia, familial breast cancer (**BRCA-2**), and hereditary nonpolyposis colorectal cancer (**Lynch**).
- Polymorphisms of the genes for **methylene tetrahydrofolate reductase** and **thymidylate synthase**.
- Family history: To first degree relatives with ca pancreas (relative risk increases 18–57 fold).
- Pancreatic cancer has **highest association with Peutz Jegher's** syndrome (**100 fold** increased risk).
- MC ductal **adenocarcinomas**; MC in the **head** of the pancreas.
- Symptoms:** **Jaundice** is the MC symptom; **Epigastric pain** that is intractable, severe, radiates to the back and may be relieved by sitting/leaning forward; **dramatic weight loss**; dyspepsia, pruritus is uncommon.
- Signs:** Obstructive jaundice, cachexia, fever, enlarged gallbladder.
- Rarer presentations:** **Thrombophlebitis migrans**; marantic endocarditis; **diabetes mellitus**; left supraclavicular lymphadenopathy (**Virchow's node**), and periumbilical lymphadenopathy (**Sister Mary Joseph's nodes**).
- Contrast-enhanced spiral CT** is the imaging modality of choice.
- CA-19-9** is elevated (not specific and sensitive enough BUT pre-op CA 19-9 levels correlate with tumor stage and post-resection it has prognostic value).
- Occult "**silvery**" blood in stool seen in **Ca ampulla of Vater**.

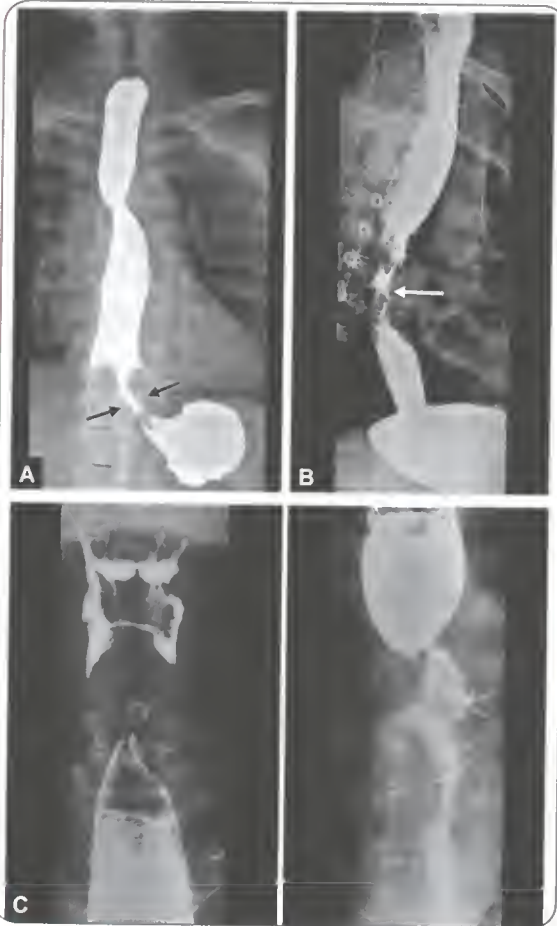
- For Ca head and uncinate process: **Modified Whipple's operation** (pylorus preserving pancreaticoduodenectomy- **PPPD**—pancreatic head, duodenum, gall bladder and distal part of bile duct are removed); post-op **pancreaticojejunostomy anastomotic leaks** are MC.
- For Ca body and tail: **Distal pancreatectomy** (including splenectomy).
- For unresectable cancer and metastatic disease: Irradiation + chemotherapy (**5-FU** or **gemcitabine**) for palliation.

CARCINOMA OESOPHAGUS

Risk factors for Ca esophagus

- Excess **alcohol** consumption, cigarette **smoking**, ingested **carcinogens** (nitrates, smoked opiates, fungal toxins), mucosal damage (from ingestion of hot **tea** or **lye**, **radiation induced** strictures), **tylosis** (palmoplantar hyperkeratosis)
- Intrinsic oesophageal disease like chronic **achalasia**, **Barrett's** oesophagus (lead to **AdenoCa**), **PLU**mmmer-Vinson syndrome (leads to **Squamous cell Ca**). "**BAD PLUS**".
- Dietary deficiencies of **selenium**, **molybdenum**, **zinc**, and **vitamin A**.
- Ca esophagus** is MC in **Lower one-third** (H'son-19th/533), more common in **men around 60 years**.
- MC histological type worldwide is **squamous cell Ca**.
- SCC affects **upper 2/3**; endemic in **Transkei** region of South Africa and in the **Asian 'cancer belt'** that extends across the middle of Asia from the shores of the Caspian Sea (in northern Iran) to China. The **highest incidence** in the world is in **Linxian** in Henan province in China.
- AdenoCa** is MC in **western countries** and in **lower 1/3**.
- Risk factors **particularly for AdenoCa** are cigarettes, obesity, Barrett's esophagus, males and GERD (Gastro-esophageal reflux disease)
- Presents with **dysphagia** (for solid foods- MC symptom), **regurgitation** (oesophageal **pseudovomiting**)
- Siewert classification** is for tumors of gastro-esophageal junction.
- Barium swallow** findings:
 - Rat tail** filling defect with **shouldered** edge
 - Mucosal irregularity**
 - Annular** irregular **stricture** - **apple core** appearance (similar to Ca colon)
- Therapy for inoperable Disease:** Radiation therapy, chemotherapy (cisplatin, paclitaxel and 5-FU), and combined therapy

- For “Curable” Disease: Surgery
 - **Radical esophagectomy** is most important aspect of curative treatment
 - **2-phase esophagectomy** (Ivor Lewis Tanner) or **3-phase esophagectomy** (McKeown) or **transhiatal esophagectomy** maybe done.
 - **Oesophageal reconstruction: MC used is stomach**, next choice is colon.
- Prognosis is determined by **T stage**.; Prognosis is poor.
- **Endoscopic ultrasound** is **best** method for **T** (Tumor size) and **N** (Lymph node) staging.



Figs. 23.2A to C: Barium swallow X-rays showing irregular filling defect at different levels—feature of carcinoma of oesophagus

MEDIASTINAL TUMORS

Location	Tumor
Anterior mediastinal tumor	Thymoma .(MC) Others - germ cell tumor; lymphoma; lipoma

Contd...

Contd...

Location	Tumor
Middle mediastinal tumor	Vascular (MC is aneurysms)
Posterior mediastinal tumor	MC is Neurogenic

EXTRA EDGE

- Overall **thymoma** is the **MC mediastinal tumor** (Bailey and Love 26th/868.). **Muller Hermalink** classification and **Modified Masaoka** staging are used for thymoma.
- **Anterior mediastinum** is MC site of extragonadal germ cell tumors.

Other Thoracic Tumors

MC benign lung tumor	Hamartoma , (pop-corn calcification on CXR)
MC benign Tumor of oesophagus	leiomyoma
MC benign chest-wall tumor	Chondroma
MC malignant chest-wall tumor	chondrosarcoma
MC benign tracheal tumor	Squamous papilloma
MC malignant tracheal tumor	Squamous cell Ca.
MC malignant Tumor of the diaphragm	fibrosarcoma
Ewing's sarcoma of the chest wall, malignant, with (t11, 22) translocation	Askin's tumor

GASTRIC CARCINOMA

Risk factors for gastric cancer

- *H.pylori* infection
- Chronic **Atrophic gastritis**
- Blood group **A**
- **Pernicious Anemia**
- **Adenomatous polyps**
- Smoking and Alcohol
- Nitrosamines in *smoked fish*
- **Menetrier's disease**
- Postantrectomy—15–20 years after Billroth II anastomosis

- More common in **Japan**, China, Chile, Ireland.
- More common in **lower socio-economic** classes—due to ingestion of partly decayed food which has exogenous bacteria which convert nitrates in *smoked/dried/salted* food to carcinogenic nitrites - BUT - **better food preservation** and **refrigeration** has **greatly reduced incidence of gastric cancer**.

Classifications

- **Lauren classification:**

Intestinal type	Diffuse type
Epidemic/Environmental etiology	Familial/endemic etiology
MC in Asia (Japan, China, Korea)	Anywhere
M>F	F>M (DiFFuse = MC in Female!)
Older age affected	Younger age affected
Preceded by precancerous lesion- intestinal metaplasia	No association with precursor lesions
Well differentiated, grow slowly and form glands	Poorly differentiated (signet ring cells), behave aggressively and scatter throughout the stomach
Distal part of stomach affected	Affects cardia/proximal part
Polypoid mass or ulcerative lesion	Infiltrates stomach wall deeply
Better prognosis	Worse prognosis
Includes Bormann type I,II,III	Includes Bormann type IV
Microsatellite instability, APC gene mutations	Decreased E-cadherin
p53, p16 inactivation	p53, p16 inactivation

- **Clinical classification:**
 - Ulcerative—ulcer through all layers
 - Superficial spreading—a.k.a ‘**early gastric cancer**’ (based on the **depth of invasion**) **most favorable prognosis**
 - **Leatherbottle type** (*linitis plastica* OR *Brinton's disease- Bormann's type IV*) – **poor prognosis**
- **Japanese classification**
 - **Early gastric cancer:** is defined as cancer limited to the mucosa and submucosa with or without lymph node involvement (T1, any N).
- The prognosis of **gastric carcinoma** is related to the stage of the disease at the time of diagnosis and to the histologic grade of the carcinoma. Staging is by TNM staging.
 - This can be either protruding, superficial or excavated. Very curable.
 - **Advanced** gastric cancer: involves **muscularis**.
- **WHO classification**

- Five types: (1) **tubular** (2) **papillary** (3) **mucinous** (4) **poorly cohesive** Ca (including signet ring cell Ca) and (5) **Mixed** Ca
- **Other classification systems** are: **Ming** classification;; **Borrmann's** classification and **Goseki** classification.
- **Note:** Lauren's also includes a **mixed type**.

Clinical Features

- MC is **adenocarcinoma** (intestinal type MC than diffuse type).
- MC site is **proximal third of stomach** (including the oesophagogastric junction).
- **Symptoms:** Dyspepsia lasting longer than a month in patients > 40 years; weight loss and the 3 As— Anaemia (iron deficient), Anorexia, Asthenia.
- Diagnosis – **endoscopy with multiple biopsies** (most accurate).
- **Iron deficiency anemia** due to **chronic blood loss** or **anemia of chronic disease** may occur.
- Unusual clinical features associated with gastric adenocarcinomas include *migratory thrombophlebitis*, *microangiopathic hemolytic anemia*, *diffuse seborrheic keratoses* (so-called *Leser-Trelat sign*), and *acanthosis nigricans*.
- **Eneterogastric reflux** plays a major role in **gastric stump Ca**.

TNM Staging of Gastric Cancer

- The prognosis of **gastric carcinoma** is related to the stage of the disease at the time of diagnosis and to the histologic grade of the carcinoma. Staging is by TNM staging:

T stage
T0: Carcinoma in situ, intra-epithelial tumor
T1: Tumor extension to submucosa
T2: Tumor extension to the muscularis propria or subserosa
T3: Tumor penetration of the serosa
T4: Tumor invasion of the adjacent organs.
N stage
N0: No lymph nodes involved
N1: Metastases in 1–6 regional lymph nodes
N2: Metastases in 7–15 regional lymph nodes
N3: Metastases in > 15 regional lymph nodes.
M stage
M0: No distant metastases
M1: Distant metastases.

Treatment

- **Surgery:** Complete surgical removal of the tumor with resection of adjacent lymph nodes offers the only chance for cure. However, this is possible in less than a third of patients.
 - A subtotal gastrectomy is the treatment of choice for patients with distal carcinomas,
 - Total gastrectomies are required for more proximal tumors.
- Chemotherapy: Cisplatin combined with epirubicin/docetaxel and infusional 5-FU or capecitabine, or with irinotecan.
- Relatively **radioresistant** tumor.
- Prognosis **poor**.

Metastases from gastric cancer

- **Lymphatic spread:** to supraclavicular node (**Virchow's node, Troisier's sign**).
- **Hematogenous spread:** **Liver** is the MC site for of tumor.
- **Transperitoneal spread**
 - To the ovary (**Krukenburg's tumor** — classically from colloid Ca); **transcoelomic** spread
 - To periumbilical region ("**Sister Mary Joseph node**"),
 - To peritoneal cul-de-sac/pouch of Douglas (rigid **Blumer's shelf** palpable on rectal or vaginal exam);
 - **Peritoneal dissemination** of gastric cancer (peritoneal carcinomatosis) is best detected by **laparoscopy**.

Gastric Polyps

- MC type is **metaplastic polyp** (a/w *H. Pylori* infection);
- **Fundic gland polyps** (a/w **proton pump inhibitors**) — both of these don't have malignant potential;
- **True adenomas** however have **malignant potential**.

Primary Gastric Lymphoma

- The **stomach** is the **MC extranodal location** for lymphoma.
- Second MC gastric malignancy; usually **solitary**;
- MC are **non-Hodgkin B cell lymphomas**
- MC arises from MALT (mucosa associated lymphoid tissue);
- **H. pylori** infection increases the risk.
- **Treatment:** Antibiotic for **H. pylori eradication**; surgery + chemotherapy (CHOP + **rituximab** regimen).

GASTROINTESTINAL STROMAL TUMORS

- MC mesenchymal tumor of GIT.
- GIST is MC in the **stomach** (66%); but occur throughout the GIT.

- Maybe a/w **neurofibromatosis**.
- **GIST** originate from **interstitial cells of Cajal**.
- GIST are a/w mutations in **KIT, a receptor tyrosine kinase**.
- Most GIST stain positively for **CD117** (part of the KIT protein); **high CD117** means **high malignant potential**.
- Usually asymptomatic; GIST may be discovered incidentally; may cause **bleeding** (hematemesis, melena) and abdominal pain..
- **Endoscopic U/S** (possibly with guided FNA biopsy) is the optimal study.
- On **endoscopic U/S** - **benign lesions** are **smaller than 2 cm, have a smooth border, and have a homogeneous echo pattern**.
- **Surgery** is recommended for **all patients** with tumors that are symptomatic; or for risk of malignancy.
- Treatment: **Tyrosine kinase inhibitor imatinib mesylate**; if resistant may respond to **sunitinib**.
- Best-documented **prognostic markers** are **tumor size** and **mitotic activity**.
- For treatment refractory GIST; **Regorafenib** is now approved.

"Carney"

- **Carney's triad:** **GIST, pulmonary chondroma, and/or functioning extra-adrenal paraganglioma**.
- **Carney's syndrome:** **GIST, paraganglioma** and germline mutation of **succinate dehydrogenase**.

BENIGN TUMORS OF THE SMALL INTESTINE

- Benign small bowel neoplasms include **adenomas, lipomas, hemangiomas and neurogenic tumors** — can present with **intussusception, small bowel obstruction** and bleeding.

Peutz-Jeghers syndrome

- **AD (STK11 gene on chr 19)**.
- **Mucocutaneous melanin deposits** (on face, lips, oral mucosa, palms and soles)
- Small intestinal (**usually jejunal**) **hamartomas (juvenile polyps)** - malignant change is **very rare**;
- Tumors of the **ovary, breast, pancreas and endometrium** may be associated.

MALIGNANT TUMORS OF THE SMALL INTESTINE

1. **Adenocarcinoma:** MC primary Ca of the small intestine and occurs MC at the ampulla of Vater; Surgical resection is the treatment of choice.

2. Lymphoma:

- Primary intestinal lymphomas (**western** type): **Non-Hodgkin's B cell lymphomas**.
 - **T cell lymphomas** are a/w **celiac disease**.
 - **Mediterranean lymphoma:** In the Middle East, lymphomas also may arise in the setting of **IPSID** (immunoproliferative small intestinal disease); **alpha heavy chains** in the serum is seen in 70%; this is a B cell tumor.
 - **Burkitt's lymphoma** in children can affect **ileocecal region**.
- ## 3. Carcinoid tumors:
- These occur throughout the GIT, in the following frequency: **appendix > ileum > rectum** (Also, carcinoid is MC tumor of appendix). Small tumors of **neuroendocrine cells**.
 - **Small intestinal carcinoids:** MC arise in the distal ileum (from argentaffin (Kulchitsky) cells in the crypts of Lieberkuhn).
 - Carcinoid syndrome is due to high levels of **serotonin (5-HT)**; also seen — ↑ **5-HIAA** in urine; ↑ serum Chromogranin A. Other secretory products of carcinoids = **histamine, bradykinin, kallikrein and prostaglandins**.
 - Clinically: Characterized by **cutaneous flushing, palpitations, abdominal pain, diarrhea, bronchospasm, and right-sided heart failure (tricuspid regurgitation)** and eventually **tricuspid and pulmonic stenosis**.
 - Optimal initial imaging study is **somatostatin receptor scintigraphy**.
 - **Rule of 1/3s:** 1/3 metastasize (**MC to liver**); 1/3 present with second malignancy; 1/3 are multiple.
 - Treatment: **Surgical** resection is curative in localized disease; **octreotide** for symptomatic control.

TUMORS OF THE LARGE INTESTINE

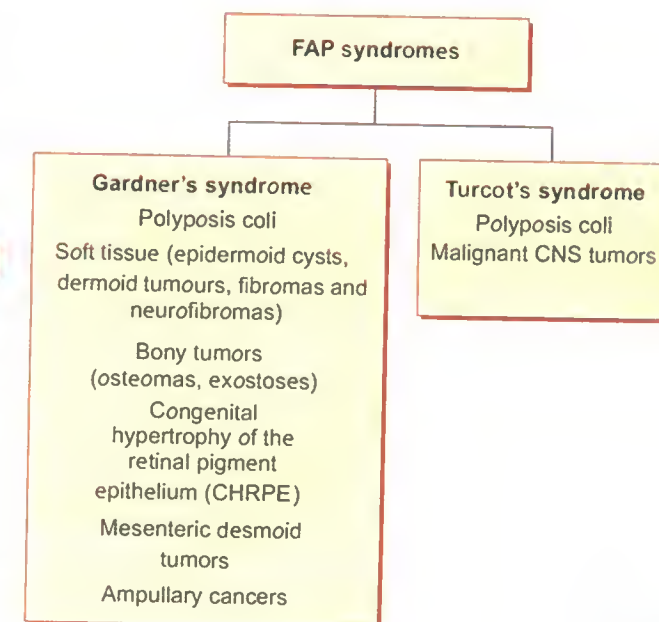
Nonfamilial Adenomatous Polyps

- Histologically adenomas are classified as **tubular, tubulovillous and villous**.
- Their significance is that most cases of adenocarcinoma of the colon are **believed to arise from adenomas**. It is proposed that there is an adenoma - carcinoma sequence whereby colorectal cancer develops through a continuous process from **normal mucosa to adenoma to carcinoma**.

- Villous adenoma can cause diarrhea, mucus discharge, hypokalemia and hypoalbuminemia.
- ↑ size of adenoma = ↑ risk of malignancy; adenomas > 5mm in dia are excised due to their malignant potential.
- Most adenomatous polyps are amenable to safe **colonoscopic removal**.

Familial Adenomatous Polyposis Coli (FAP)

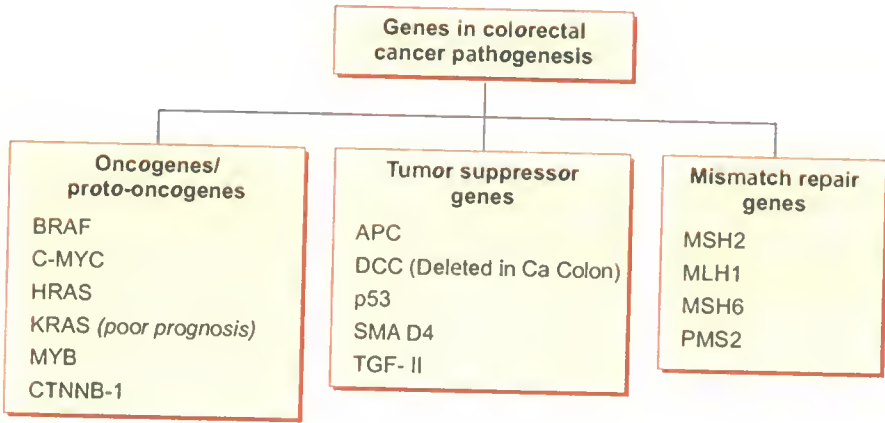
- FAP is an **AD** disease characterized by the development of > **100 colorectal** adenomas and various extracolonic features.
- It is due to a defect in the **adenomatous polyposis coli gene (APC)**, which is located on **chromosome 5q**.
- Polyps are rare before 16 years, and almost all affected individuals have adenomas by age 35 years. **Colon cancer is inevitable (100%)** by age 40 unless **prophylactic colectomy** is performed.
- Fundoscopy reveals blackspots (congenital hypertrophy of the retina - **CHIRPES**) and is valuable in detecting carriers of the gene.
- **Sulindac** or **celecoxib** can decrease the number and size of polyps; only **temporary effect**.
- **Colectomy** remains the primary therapy in patients with polyposis coli.
- Genetic testing of at risk family members in early teens; Examine at age 10-12 years and yearly thereafter; If no polyps at age 20 then 5-yearly exam till age 50.



COLORECTAL CANCER

Risk Factors

Age	Personal history	Family history	
		Colorectal cancer or adenomatous polyps	Hereditary syndromes (AD)
▪ > 50 years	▪ Tobacco use ▪ Previous colorectal cancer ▪ Adenomatous polyps ▪ IBD (particularly ulcerative colitis) ▪ Streptococcus bovis bacteremia ▪ Ureterosigmoidostomy ▪ Decreased dietary fibre, increased red meat consumption	▪ One first degree relative < 60 years of age or 2 first degree relatives of any age	▪ Familial Adenomatous Polyposis coli (responsible for 85% colon cancers)
			▪ Nonpolyposis coli syndrome (Lynch synd.) —also a/w endometrial, ovarian, stomach and small intestinal tumors, AD , a/w cancer of proximal colon) ▪ MYH associated polyposis ▪ Cowden, Peutz Jegher; Ruvalcaba Smith Myhre syndrome



Molecular Pathogenesis of Colorectal Cancer

- **Microsatellite instability** pathway (15%): DNA mismatch repair gene mutations → sporadic and HNPCC syndrome. Mutations accumulate, but no definite morphologic correlates.
- **APC/beta-catenin** (chromosomal instability) pathway (85%)

Clinical features of Ca colon

- A: Invasion of but not breaching the muscularis propria
- B: Breaching the muscularis propria but not involving lymph nodes
- C: Lymph nodes involved
- D: Metastases (stage D introduced later, not by Duke)
- These are MC **adenocarcinomas** and approximately half arise in the **rectosigmoid region**.
- **Liver** is the **MC site of metastases**; transcaefomic spread can also occur.
- **Carcinoembryonic antigen** (CEA) levels are elevated; after complete surgical resection, CEA levels should

- normalize; rise in CEA levels that had normalized initially after surgery is suggestive of cancer recurrence.
- **Colonoscopy** is the **investigation of choice**.
- **Surgical resection** is the **treatment of choice** for virtually all patients who have resectable lesions and can tolerate general anesthesia.
- NSAIDs (*aspirin, celecoxib and sulindac*) may be protective.
- **Staging used—TNM (currently used) and Duke's classification (old)**; others are *cunderson Sosin* and *Astler Coller*.
- **Amsterdam criteria** are used in diagnosis of **HNPCC**.

Dukes' staging for colorectal cancer

- A: Invasion of but not breaching the muscularis propria
- B: Breaching the muscularis propria but not involving lymph nodes
- C: Lymph nodes involved
- D: Metastases (stage D introduced later, not by Duke)

TNM Classification for Colonic Cancer

T stage
T1: Into submucosa T2: Into muscularis propria T3: Into pericolic fat or sub-serosa but not breaching serosa T4: Breaches serosa or directly involving another organ
N stage
N0: No nodes involved N1: 1–3 nodes involved N2: Four or more nodes involved
M stage
M0: No metastases M1: Distant metastases

- Adjuvant chemotherapy:
 - **Stage III** disease: a combination of oxaliplatin, fluorouracil, and leucovorin (FOLFOX).
 - **Stage IV**: Currently, either **FOLFOX** or **FOLFIRI** (fluorouracil, and leucovorin and irinotecan) is the preferred first-line treatment regimens for most patients with metastatic colorectal cancer.
 - **Cetuximab, panitumumab (anti EGFR) and bevacizumab (anti VEGF)** may be used
 - Bevacizumab (Avastin) may cause serious **thromboembolic events** (including stroke and myocardial infarction) in 5% of patients.

CANCER OF THE ANUS

- MC is **squamous cell cancer (distal to pectinate line)**.
- Cancer arising proximal to pectinate line may be basaloid, cuboidal or cloacogenic.
- Risk factors are **chronic anal irritation, condyloma acuminata (HPV), perianal fissures, chronic hemorrhoids and leukoplakia, HIV infection**.
- Occur MC in middle aged individuals, F > M.
- Treatment:
 - Historically, early anal margin tumors were treated by local excision and anal canal tumors by abdominoperineal resection of the rectum.
 - **Nowadays primary treatment** is by **chemoradiotherapy (combined modality therapy, Nigro)**, the chemotherapy usually including a combination of 5-fluorouracil with mitomycin C or cisplatin.

RENAL CELL CARCINOMA

Risk factors

- Cigarette smoking
- Acquired cystic disease of the kidney a/w end stage renal disease
- Tuberous sclerosis
- Polycystic kidney disease
- von Hippel-Lindau disease

Pathology of Renal Cell Ca (RCC)

Subtype of RCC	Familial and Genetic factors	Pathological features	Other characteristics
Clear cell RCC (75%)	▪ Von Hippel-Lindau disease (VHL gene - 3p) mutation, deletion or hyper-methylation) ▪ Tuberous sclerosis ▪ Gain of chromosome 5q	▪ Well-circumscribed, lobulated , golden yellow tumor with foci of necrosis and hemorrhage ▪ Hypervascular tumor ▪ Clear vacuoles contain both lipid and glycogen. IHC: ▪ Low-molecular-weight cytokeratin (LMWCK).	▪ Originate from proximal tubule ▪ HYPERvascular pattern seen on contrast enhanced MRI ▪ Tumor shrinkage common with targeted molecular therapy ▪ Vascular invasion is common ▪ Bleeding from CNS metastases is common with anticoagulation (do MRI before starting anti-coagulants)
Papillary RCC (10%)	▪ Type 1: HPRCC (hereditary papillary RCC syndrome). ▪ Type 2: HLRCC (hereditary leiomyomatosis and RCC syndrome). ▪ Trisomy of chromosome 7 and 17 ▪ Loss of Y chromosome ▪ Activation of c-MET oncogene (7q) by mutation	▪ Fleshy tumor with fibrous pseudocapsule with foci of necrosis and hemorrhage ▪ Papillary structures with single layer of cells around fibrovascular cores ▪ Type 1 - basophilic ; Type 2 - eosinophilic IHC ▪ LMWCKs , CK7 (type 1 >type 2), AMACR	▪ Originate from proximal tubule ▪ Commonly multicentric ▪ A/w ARCD (<i>acquired renal cystic disease</i>) and ESRD (End Stage Renal Disease) ▪ Type 1: good prognosis. ▪ Type 2: worse prognosis

Contd...

Subtype of RCC	Familial and Genetic factors	Pathological features	Other characteristics
Chromophobe RCC (5%)	<ul style="list-style-type: none"> Extensive loss of entire chromosomes Fumarate hydratase gene (1q) mutation 	<ul style="list-style-type: none"> "Plant cells" with pale cytoplasm, perinuclear clearing or "halo," nuclear "raisins," and prominent cell borders. Positive Hale colloidal iron staining 	<ul style="list-style-type: none"> Originate from intercalated cells of collecting duct Best prognosis Birt-Hogg-Dubé syndrome (a/w ocnocytomas)
Bellini duct (collecting duct) carcinoma (<1%)	<ul style="list-style-type: none"> Multiple chromosomal losses. 	<ul style="list-style-type: none"> Complex, highly infiltrative cords within inflamed (desmoplastic) stroma; high-grade nuclei, mitoses 	<ul style="list-style-type: none"> Originate from collecting duct Worse prognosis
RCC a/w Xp11 translocation	<ul style="list-style-type: none"> Various mutations involving chromosome Xp11.2 resulting in TFE3 gene fusion. 	<ul style="list-style-type: none"> Well-circumscribed tumor. Variable; often clear cells with papillary architecture. 	<ul style="list-style-type: none"> Occur in children and young adults Accounts for 40% of pediatric RCC Indolent course
Renal medullary carcinoma (rare)	<ul style="list-style-type: none"> A/w sickle cell trait 	<ul style="list-style-type: none"> Infiltrative, gray-white; extensive hemorrhage and necrosis. Poorly differentiated cells with lacelike appearance 	<ul style="list-style-type: none"> Originate from collecting duct. Affects in 2nd and 3rd decades Worst prognosis

- Renal Cell Carcinoma**; a.k.a: **Hypernephroma**, **Grawitz Tumor**
- M:F = 2:1**
- Originates from proximal tubule cells**
- MC** occurs at the **upper pole of kidney**
- MC** type is **adenocarcinoma**
- Spread: it is **prone to grow into the renal vein**; may also be seen in the lungs as **cannonball metastases**.
- CT scanning** is the **most valuable** imaging test for renal cell carcinoma.
- MRI and duplex Doppler ultrasonography** are excellent for detecting tumor within the renal vein or vena cava.
- Increased ESR** is present in almost **55% patients** of renal cell Ca.
- Robson system and AJCC system** is used for staging renal cell carcinoma.

Staging of RCC

- Stage I:** Tumors are confined to the kidney
- Stage II:** Tumors extend through the renal capsule but are confined by Gerota's fascia;
- Stage III:** Tumors involve the renal vein or vena cava (stage IIIA) or the hilar lymph nodes (stage IIIB) and
- Stage IV:** Tumors that are locally invasive to adjacent organs (excluding the adrenal gland) or distant metastases.

- Primary Treatment: Stage I and stage II tumor and selected cases of stage III disease is **radical nephrectomy**.
- RCC responds poorly to chemotherapy and radiotherapy; **Vinblastine** is the single most effective agent; **alpha interferon** and **IL-2** have shown promising results.
- Spontaneous regressions** have been reported anecdotally.

Transitional Cell Cancer of the Renal Pelvis and Ureter

- Ureteral neoplasms** are **MC** located in the **distal third of the ureter**
- Risk factors are **cigarette smoking**, **hydrocarbon exposure**, **chronic phenacetin abuse** and with **Balkan nephropathy** (a chronic interstitial nephritis endemic in Bulgaria)
- The MC symptom is a **painless gross hematuria**.
- Treatment is usually by **nephroureterectomy**.

Squamous Cell Carcinoma of the Renal Pelvis

- This is rare and often a/w **chronic inflammation** and **leukoplakia** resulting from renal stone.
- The tumors are **radiosensitive**, BUT **metastasize** at an early stage and the prognosis is poor.

BLADDER CANCER

3 Types of bladder cancer

- Transitional cell carcinoma** is MC; a/w **cigarette smoking**, exposure to **industrial dyes**; chronic **cyclophosphamide** exposure.
- Pure squamous cell carcinoma**: tend to be solid and nearly always associated with muscle invasion. A/w chronic **Schistosoma haematobium** exposure, chronic irritation by **vesical calculi**, **leukoplakia** of bladder and chronic **catheter** use.
- Pure adenocarcinoma** usually arises in the fundus of the bladder at the site of **urachal remnant**.

- Superficial type** (not invading muscle) is MC.
- Painless gross hematuria** is the MC symptom and should be regarded as indicative of bladder carcinoma until proven otherwise. (Note: **Microscopic hematuria** is MC due to prostate origin; **Benign cystitis** is the MC cause of **gross hematuria**)
- Superficial disease**: complete **transurethral resection + intravesical therapy with BCG** (best accepted); Other intravesical agents = **doxorubicin**, **thiotepa** and **mitomycin C**.
- Muscle infiltrating tumors**: radical cystectomy +/- systemic chemotherapy.
- Post surgery urinary diversion**: Urinary diversion through **Ileal conduit (MC)** to the skin where it is collected in external appliance; Currently, most patients receive either a **continent cutaneous reservoir** constructed from detubularized bowel or an **orthotopic neobladder**.
- When a segment of jejunum is used for a conduit a syndrome of **hyperkalemic hypochloremic acidosis** with hyponatremia and uraemia has been reported.
- In patients who have undergone **ureterosigmoidostomy**, a **hypokalemic, hyperchloremic acidosis** occurs.
- Treatment of metastatic disease is by chemotherapy, **M-VAC**—Methotrexate, Vinblastine, doxorubicin (Adriamycin), and Cisplatin.

PROSTATE CANCER

- MC malignant tumor in **men > 65 years**.
- The contemporary classification of the prostate into different zones (**peripheral zone – carcinoma** arises; **periurethral zone – BPH** arises) was based on the work of **McNeal**.
- MC type is **adenocarcinoma** that arises in the **prostatic acini**, usually in the '**peripheral**' zone of the prostate.

- Symptoms: **asymptomatic** (both early and advanced Ca prostate); large or locally extensive prostatic cancers can cause **obstructive voiding symptoms**.

Investigations

Prostate specific antigen (PSA)

- PSA is a **Kallikrein related protease, glycoprotein**
- PSA serum level is the **most sensitive test** for early detection of prostate cancer
- Normal upper limit is 4 ng/ml.
- Prostate confined cancers** are a/w levels < **10 ng/ml** whereas **metastatic disease** may be a/w > **30 ng/ml**.
- PSA elevation can also occur with BPH, prostatitis, prostatic infarction and after prostate biopsy).
- PSA doubling time is also called **PSA velocity**.
- A decrease in PSA to the normal range following hormonal ablation is a good prognostic sign

- Ultrasound**: Prostate on US is best visualized by transrectal US (TRUS) with a High frequency transducer (> 7 MHz); On TRUS, carcinoma is revealed as **hypoechoic** densities within the peripheral zone.
- Biopsy**: **Transrectal Ultrasound guided prostatic biopsy** (with spring loaded 18-gauge biopsy needle) is **gold standard for diagnosis**. **12 core biopsies** are obtained.
- The **Gleason score (2–10)** is based on histologic pattern of glandular differentiation
- MRI** with an **endorectal coil** is superior to CT to detect cancer and assess local spread. **Best method** to stage (TNM staging) the tumor.

Metastases

- Hematogenous metastases** occur to **bone (osteoblastic)**-MC to **lumbar spine (axial skeleton)** - leading to **pathologic fractures**. (Robbins, 8th/998)
- Lymph node metastases** can lead to lower extremity lymphedema.
- The **TNM staging** scheme has replaced the **Whitmore-Jewett system**.
- The route of lymphatic spread (in decreasing order) is to obturator, internal iliac, common iliac, presacral and para aortic nodes.

TNM Staging of Prostate Cancer

- | | |
|-----------|--|
| T1 | Clinically inapparent tumor, neither palpable (by digital rectal exam, DRE) nor visible by imaging |
|-----------|--|

Contd...

Contd...

T1a	Tumor incidental histologic finding in ≤5% of resected tissue; not palpable
T1b	Tumor incidental histologic finding in >5% of resected tissue
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate
T2a	Tumor involves half of one lobe or less
T2b	Tumor involves more than one half of one lobe, not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles and/or pelvic wall
N1	Positive regional lymph nodes
M1	Distant metastases

Treatment

- **Treatment of localized disease (T1 and T2):** Both radiation therapy and radical prostatectomy allow for acceptable levels of local control.
- **Radical Prostatectomy:** Here, the seminal vesicles, prostate, and ampullae of the vas deferens are removed. Ideal candidates for the procedure include healthy patients with stages T1 and T2 prostatic cancers.
- **Radiotherapy:** in the form of external beam therapy, interstitial brachytherapy, intensity modulated radiation therapy (IMRT) may be used.
- **T3 and T4:** Early androgen ablation.
- **Bone-seeking radiopharmaceuticals** like ⁸⁹Sr or diphosphonates unlabelled or labelled with samarium (¹⁵³Sm) can be of benefit in the **control of pain** even in the absence of objective response of the tumor.
- The **CAPRA** nomogram and **Kattan** nomogram are used for surveillance
- For **metastatic disease**, **androgen ablation** is used as in below table
- Other drugs for metastatic disease: **Denosumab**, a RANK ligand inhibitor, **Docetaxel**, **Sipuleucel-T**, an autologous cellular immunotherapy, cabazitaxel and abiraterone **Cabozantinib** (is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2), and alpharadin (radium-223 chloride).

Androgen Deprivation for Prostatic Cancer

Level of action	Agent	Sequelae
Pituitary, hypothalamus	Diethylstilbestrol	Gynecomastia, hot flushes, thromboembolic disease, erectile dysfunction
	LHRH agonists (Leuprolide, goserelin)	Erectile dysfunction, hot flushes, gynecomastia, rarely anemia
	LHRH antagonist (Degarelix)	Hot flushes, weight gain, erectile dysfunction, increased liver function tests
Adrenal	Ketoconazole	Adrenal insufficiency, nausea, rash, ataxia
	Amino-glutethimide	Adrenal insufficiency, nausea, rash, ataxia
	Corticosteroids	Gastrointestinal bleeding, fluid retention
Testis	CYP171A inhibitor (Abiraterone)	Weight gain, fluid retention, hypokalemia, hypertension
	Orchiectomy	Gynecomastia, hot flushes, erectile dysfunction
Prostate cell	Antiandrogens (Flutamide, Bicalutamide)	No erectile dysfunction when used alone; nausea, diarrhea

TESTICULAR CANCER

Risk Factors

- **Cryptorchidism** (undescended testis): **abdominal testes > inguinal testes**
- **Testicular feminization** synd
- **Klinefelter's** syndrome.

Pathological Classification

1. **Germ cell tumors - MC 90%;** these include
 - **Seminoma (35%)**
 - **Non-seminoma (65%)**—see types below.
2. **Interstitial tumors** (include **Leydig cell** tumors that masculinizes and Sertoli cell tumor that feminizes).
3. **Lymphoma**

Seminoma

- Seminoma is **MC on right side**
- **MC bilateral primary testicular** tumor = **Seminoma**
- A seminoma typically has a cut surface which is homogeneous and pinkish cream in color.

- Metastasize mainly via **lymphatics** to **para aortic nodes**.
- For **seminoma**, the **MD Anderson system of staging** is commonly used.

Non-Seminomatous Germ Cell Tumors (NSGCT)

The usual type of teratoma is yellowish in color with cystic spaces containing gelatinous fluid. Types of NSGCT:

- **Embryonal carcinoma:** **Highly malignant** tumors that occasionally **invade cord structures**.
- **Yolk sac tumor:** Tumors secrete **AFP**.
- **Choriocarcinoma:** Tumors secrete **HCG**; **highly malignant** tumor that metastasizes early via BOTH the lymphatics and bloodstream.
- **Teratoma:** These tumors contain more than one cell type with components derived from **ectoderm, endoderm, and mesoderm**.

Clinical Features:

- **MC symptom** of testicular cancer is **painless enlargement of the testis**.
- Diagnosis is confirmed by ultrasound scanning of the testis.
- Tumor markers: **hCG, AFP, LDH**.
- **Chest X-ray** may show **cannonball** metastases.

Staging (Older staging)

- Stage I: The tumor is confined to the testis
- Stage II: Nodal disease is present but is confined to nodes below the diaphragm
- Stage III: Nodal disease is present above the diaphragm;
- Stage IV: Nonlymphatic metastatic disease (most typically within the lungs).

TNM Staging

T stage
T1: Tumor limited to testis and epididymis; may invade tunica albuginea but NOT tunica vaginalis; NO vascular or lymphatic invasion
T2: Tumor limited to testis and epididymis WITH involvement of tunica vaginalis WITH vascular or lymphatic invasion
T3: invasion of spermatic cord
T4: invasion of scrotum
N stage (Retroperitoneal Lymph Node - RPLN)
N1: One or more RPLN involved but all <2 cm in greatest dimension
N2: One or more RPLN involved 2–5 cm in greatest dimension
N3: One or more RPLN involved >5 cm in greatest dimension
M stage
M0: No metastases
M1: Distant metastases

Treatment

- Stage I seminoma: **Orchiectomy** and radiotherapy
- Stage I NSGCT: Chemotherapy (BEP regimen - Bleomycin; Etoposide, cis-Platinum)
- Stage II-IV tumors: Combination chemotherapy (BEP) is mainstay of treatment.

EXTRA EDGE

- In **men > 50 years**, **lymphoma is the MC testis tumor**, and overall it is the **MC secondary neoplasia of the testis**.
- Testicular tumors in **children** are usually **onoplastic teratomas**. They occur **before the age of 3 years** and are usually **fatal**
- **Metastases to testis** are RARE and MC occurs from **Colorectal**.

CANCER OF PENIS

Risk factors for Ca penis

- Phimosis
- Chronic balanoposthitis
- Penile warts
- Buschke Lowenstein tumor (verrucous Ca, locally invasive but NO metastases).
- BXO—Balanitis Xerotica Obliterans
- Leukoplakia

Ca in Situ of Penis

- A red cutaneous patch on the penis—A.k.a **Bowen's disease** (when it occurs on the **shaft of penis**) or **erythroplasia of Queyrat** (when it occurs on **glans penis**).
- Treatment is by topical 5-FU cream; CO2 laser ablation or surgical excision.

Clinical Features

- Presents in **6th decade** of life.
- **Squamous cell Ca** is **MC type**; MC originates from **glans penis**.
- Growth on penis with **foul bloody discharge**; little or **NO pain** present.
- **50%** have **inguinal lymph nodes** enlarged at presentation.
- **MC cause of death** is **erosion of femoral vessels** by metastatic inguinal lymph nodes.
- TNM staging and **Jackson's staging** methods are used.

Staging

T1: tumors are confined to the skin (glans or prepuce)

T2: tumors invading the corpus spongiosum or the corpus cavernosum
T3: tumors invade the urethra
T4: tumors invade adjacent structures.
N1 and N2 disease: spread to inguinal lymph nodes
N3 disease: spread to iliac nodes

Treatment

- **Circumcision** immediately after birth confers immunity against Ca penis but NOT if done later in life.
- For primary lesion **surgery is mainstay** of treatment (partial or total penectomy).
- Enlarged inguinal nodes should be treated with **antibiotics for 3 weeks** after surgery of primary lesion.
- Sentinel lymph node biopsy (**CABANA** procedure) is done for inguinal node status.

BRAIN TUMORS

Must Know about Brain Tumors

MC brain tumor overall	Metastases to brain
MC primary brain tumor in adults	Meningioma (H'son 19th/602)
MC primary malignant brain tumor in adults	Glioblastoma multiforme
MC primary brain tumor in children	Pilocytic astrocytoma (a type of glioma)
MC primary malignant brain tumor of childhood	Medulloblastomas
Adult primary brain tumors are mainly	Supratentorial ("Adults are Above!")
Childhood primary brain tumors are	Infratentorial

WHO Classification of Brain Tumors

Neuroepithelial tumors	<ul style="list-style-type: none">• Gliomas<ul style="list-style-type: none">- Astrocytoma (see below)- Oligodendroglioma- Ependymoma- Choroid plexus tumor• Pineal tumors• Neuronal tumors<ul style="list-style-type: none">- Ganglioglioma- Gangliocytoma- Neuroblastoma• Medulloblastoma
Nerve sheath tumors	<ul style="list-style-type: none">• Vestibular Schwannoma (See ENT chapter)
Meningeal tumors	<ul style="list-style-type: none">• Meningioma
Pituitary tumors	

Contd...

Contd...

Germ cell tumors	<ul style="list-style-type: none">• Germinoma• Teratoma
Lymphomas	
Tumor like malformations	<ul style="list-style-type: none">• Craniopharyngioma• Epidermoid tumors• Dermoid tumors• Colloid cyst

EXTRA EDGE

Astrocytomas are further divided into

- **Low grade**
 - **Grade I (pilocytic astrocytoma; subependymal giant cell astrocytoma—ventricular tumors a/w tuberous sclerosis)**
 - **Grade II (diffuse astrocytoma—Types: Fibrillary, Gemistocytic, Protoplasmic Astrocytoma)**
- **High grade**
 - **Grade III (anaplastic astrocytoma)**
 - **Grade IV (glioblastoma—previously called glioblastoma multiforme).**

Primary brain tumor associated syndromes

- Neurofibromatosis 1 (Chr 17, neurofibromin)
- Neurofibromatosis 2 (Chr 22, Schwannomin)
- Cowden's disease (CHR 10, PTEN)
- HNPCC (Lynch syndrome)
- Li-Fraumeni syndrome (Chr 17, p53)

Metastases to Brain

- **MC brain tumor overall is metastases**; small circular lesions, often multiple, usually present at grey-white matter junction.
- **MC tumor** to metastasise to brain is **Lung Ca**; others = breast, colon, melanoma, renal cell Ca, thyroid.
- **Melanoma** has the **greatest propensity to metastasize to the brain**.
- MC cause of **hemorrhagic brain metastasis** = Lung ca
- Brain mets are **MC supratentorial**.
- Treatment of choice for Brain mets = **Radiotherapy**.
- BUT Primary brain tumors **RARELY** undergo metastases.

Clinical Features and Treatment

- Clinically:
 - **Headache** (worse in morning and improves during the day)
 - **Seizures** (seen in 25% patients, focal onset)
 - Impaired cognitive function (**dementia**)
 - Motor and sensory deficits

- Raised **Intracranial pressure**.
- **MRI with contrast** is the best imaging.
- Treatment
 - Chemotherapy ± radiotherapy and resection wherever possible.
 - **Dexamethasone** is the drug of choice to **reduce brain edema**.

Adult peak incidence		
Glioblastoma multiforme (high grade astrocytoma)	MC primary malignant brain tumor in adults Present in 6th–7th decade . Highly infiltrative tumor Found in cerebral hemisphere Can cross corpus callosum Prognosis grave ; < 1 year life expectancy	Astrocytes stain for GFAP "Pseudopalisading" pleomorphic tumor cells at borders Ring enhancing lesion due to central hemorrhage and necrosis with surrounding edema (outgrows blood supply)
Meningioma	2nd MC 1° brain tumor Slow growing and benign, MC in females; a/w NF-2 MC occurs in cerebral convexities (parasagittal region); Meningiomas arise from the dura mater and are composed of neoplastic meningotheial (arachnoidal cap) cells. Resectable, Good prognosis A/w past cranial irradiation	Spindle cells concentrically arranged in whorled pattern; psammoma bodies (laminated calcifications) Imaging— hyperostosis ; extra-axial Intradural extramedullary masses with a broad dural base ; homogenous contrast enhancement ; dural tail sign, CSF vascular cleft sign ; sunburst appearance of vessels. Mother in law sign on cerebral angiography (tumor blush comes early, stays late!!). B/L acoustic schwannomas found in NF type 2
Schwannoma	Often localized to CN VIII – acoustic schwannoma A/w tinnitus and deafness Resectable	
Oligodendroglioma	Relatively rare, slow-growing; Most often in frontal lobes Chicken wire capillary pattern	Fried egg cells – round nuclei with clear cytoplasm. Often calcified
Pituitary adenoma	Prolactinoma MC Bitemporal hemianopia (due to optic chiasmal compression) and hyper/hypo-pituitarism sequelae	Rathke's pouch
Lymphoma	MC CNS Tumor in AIDS patients (100X ↑ incidence)	MRI-ring enhancing lesions difficult to distinguish from toxoplasmosis
Childhood peak incidence		
Pilocytic (low grade) astrocytoma	MC brain tumor of children . Occur typically in cerebellum/posterior fossa Usually well circumscribed; benign Good prognosis Can be surgically rescteed completely.	Rosenthal fibres – eosinophilic corkscrew fibres
Medulloblastoma	MC primary malignant brain tumor of childhood Highly malignant cerebellar tumor A form of PNET , Arises from roof of 4th ventricle; can compress 4 th ventricle causing hydrocephalus ; may seed subarachnoid space Poor prognosis; A/w Gorlin syn. (nevoid Basal cell Ca , jaw cysts) and Turcot syn.	Rosettes, or perivascular pseudorosette pattern of cells Radiosensitive Chang's staging is used. Treatment: Aggressive surgery followed by Craniospinal axis radiotherapy and Adjuvant chemotherapy— neuroendocrine abnormalities - growth hormone) deficiency MC is a known complication.
Ependymoma	From Ependymal cells of ventricle; MC in 4 th ventricle; Can cause hydrocephalus, poor prognosis	Characteristic perivacular pseudorosettes Rod shaped blepharoplasts (basal ciliary bodies) found near nucleus
Hemangioblastoma	Most often cerebellar, a/w VHL syndrome when found with retinal angiomas Can produce erythropoietin → polycythemia	Foamy cells and high vascularity

Contd...

Contd...

Adult peak incidence

Craniopharyngioma

Benign **childhood** tumor, confused with **pituitary adenoma** (can also cause **bitemporal hemianopia**)
Causes **endocrine dysfunction** (**short stature**, decreased libido, amenorrhea)
MC childhood **supratentorial/suprasellar** tumor
Pathology: Mix of solid and cystic areas; cysts contain oily fluid (blood + protein + cholesterol) - "**machinery oil**"; "**wet keratin**" nodules are seen.

Calcification is common (enamel-like)
Derived from **Rathke's pouch**

EXTRA EDGE

- WHO grading of brain tumors grades brain tumors from grade I (benign) to grade IV (highly malignant). Some important ones are
Grade I: Pilocytic astrocytoma; choroid plexus papilloma; schwannoma, meningioma, craniopharyngioma.
Grade II: Oligodendroglioma, ependymoma
Grade III: Choroid plexus carcinoma
Grade IV: Glioblastoma, medulloblastoma

SKIN CANCERS

Basal Cell Carcinoma

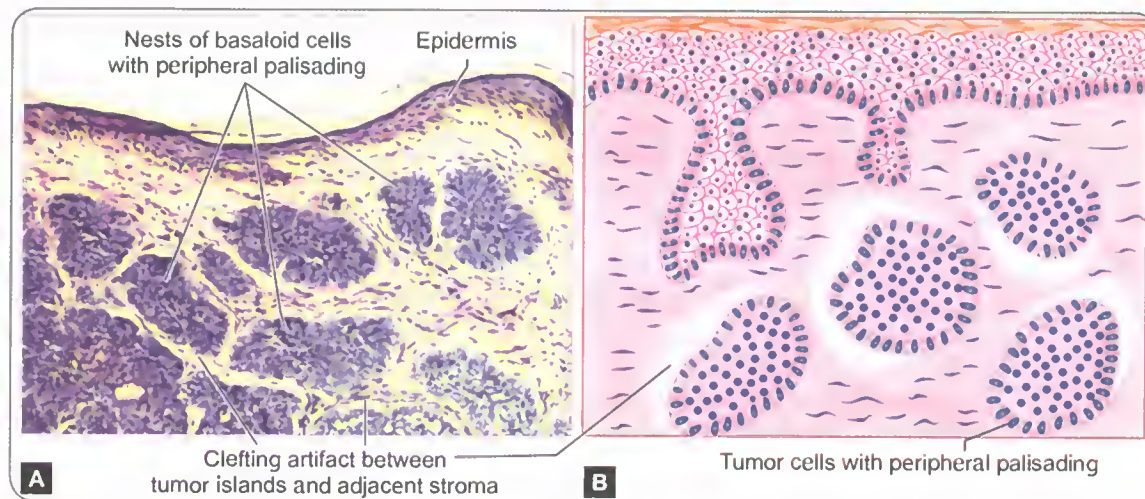
- BCC is **MC skin cancer**; a.k.a **rodent ulcer**.
- It is **locally invasive**, but **rarely metastasizing** malignant epithelioid tumor of basal cells
- Risk factors: **Short wavelength UV radiation** (290–320 nm, **sunburn rays**), X-rays and **arsenic**; Immunosuppression, **Xeroderma pigmentosum**, **Gorlin syndrome**, **Bazex syndrome**.

- Histologically**: Dermis contains irregular masses of basaloid cells having characteristic peripheral **palisaded** appearance of the nuclei.

Clinical types of BCC

- Noduloulcerative: MC type, begins as a small pearly nodule with telangiectatic vessels on its surface, may undergo ulceration, crusting, bleeding with a rolled border (rodent ulcer)
- Pigmented, Superficial (a/w arsenic exposure) and Morphoeic (scar-like)

- Treatment**: Methods used are **Mohs micrographic surgery (MMS)**, curettage and electrodesiccation and radiotherapy and cryotherapy.
- MMS**—Removal of the tumor followed by immediate frozen section histopathologic examination of margins with subsequent re-excision of tumor-positive areas and final closure of the defect—gives the **highest cure rates (98%)** and results in **least tissue loss**. (See Fig. 23.3A and B)



Figs. 23.3A and B: Basal cell carcinoma. Composed of nests of uniformly atypical basaloid cells within the dermis, that are often separated from the adjacent stroma by thin clefts. A. Photomicrograph; B. Diagrammatic

Squamous Cell Carcinoma

Etiology

- Chronic **sun exposure** in fair skinned people who **sunburn easily and tan poorly**.
- Scarring processes, chronic inflammation/infection**.
- Exposures**: Arsenic, polycyclic aromatic hydrocarbons, immunosuppression, X-ray therapy, PUVA
- Dermatoses**: Xeroderma pigmentosum, oculocutaneous albinism, DLE, Lichen planus, warts, necrobiosis lipoidica, etc.
- Persistent **heat injury** (**erythema ab igne**, '**kangri**' cancer), **Bowen's disease**, **leukoplakia**, **actinic keratosis**.

Presentation

- SCC, MC arises on **sun-exposed areas** like face, pinna, back of hands; AND on **mucocutaneous junctions** such as on the lips, anal canal and glans penis.
- This presents as an ulcerated lesion with **indurated raised edges**.

Histology

- Well-differentiated SCCs have whorled arrangement of malignant squamous cells forming "**horn pearls**" or "**keratin pearls**".
- Tumors a/w **actinic keratoses** have a **lower metastases**.
- Regional lymph nodes** are the **MC site** of metastases.

Treatment

- Wide excision** is the **treatment of choice**, once the diagnosis is confirmed by biopsy.
- Mohs micrographic surgery** provides a > 90% cure rate for SCC and is useful in **SCC with perineural invasion**.

EXTRA EDGE

- Multiple SCC** are very common on the **sun-exposed skin of organ transplant patients**.
- Voriconazole** treatment a/w increases risk of development of **SCC**, especially in **lung transplant patients**.
- Important D/D of SCC = **keratoacanthoma**—a fast-growing, benign, self-limiting papule plugged with keratin. (See Fig. 23.4A and B)

Malignant Melanoma

- Melanoma is a malignancy of pigment-producing cells (melanocytes) occurring in the **skin, eyes, ears, GI tract, leptomeninges of the central nervous system (CNS), and oral and genital mucous membranes**.

Risk factors for melanoma

- Total body nevi (higher number = higher risk)
- Family or **personal history**
- Dysplastic** nevi
- Giant **congenital melanocytic nevus**
- Light skin/hair/eye color
- Poor tanning ability
- Freckling
- UV exposure/sunburns/tanning booths
- CDKN2A, CDK4, MITF** mutation; MC1R variants
- Xeroderma pigmentosum** and **familial atypical mole melanoma synd.**

- A **changing mole** is the **MC symptom of melanoma**. A mole that stands out from the patient's other moles deserves special scrutiny—the "**ugly duckling sign**."
- ABCDE criteria** for a changing mole: **A**symmetry; **B**order irregularity and **B**leeding; **C**olor variegation, **D**iameter >6 mm; **E**volving (change in size/shape/color/: **i**itchiness, **c**rusting)

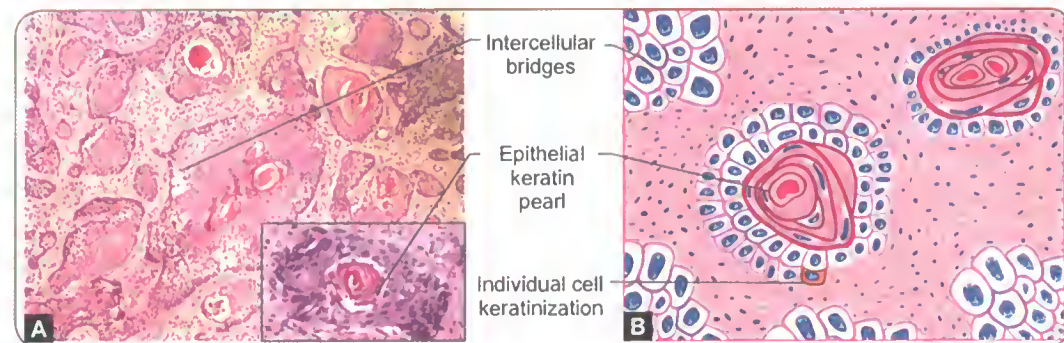
Clinical histopathologic subtypes

- Superficial spreading melanoma: MC subtype of melanoma; seen on intermittently sun exposed skin
- Nodular melanoma: Rapid growth; worst prognosis.
- Lentigo maligna melanoma (Hutchinson's freckle): Essentially a malignant melanoma in situ and has a good prognosis.
- Acrall lentiginous melanoma: Least common subtype; occurs on the palms, soles, or beneath the nail plate; pigment spread to the proximal or lateral nailfolds (Hutchinson sign); MC in blacks, east Asians
- Amelanotic melanoma: Nonpigmented; MC occurs in the setting of melanoma metastasis to the skin.
- Desmoplastic melanoma, is a/w fibrotic response, neural invasion, and a greater tendency for local recurrence.

- The **best predictor of metastatic risk** is the lesion's **Breslow thickness**.
- The prognostic scheme based on anatomic level of invasion (**Clark level**)—NO longer used..
- An **excisional biopsy** is the **preferred** technique.
- AJCC staging: stages I and II (localized cutaneous disease); **Stage III** involves the regional lymph nodes, and **stage IV** disease includes distant skin, subcutaneous, nodal, visceral, skeletal, or CNS metastasis.

Treatment

- Surgery is the **primary mode** of therapy for localized cutaneous melanoma.
- Interferon alpha** and **Interleukin-2**.
- Hyperthermic isolated limb perfusion** - regional chemotherapy.



Figs. 23.4A and B: A. Photomicrograph; B. Diagrammatic; Well-differentiated squamous cell carcinoma composed of polygonal squamous tumor cells arranged in orderly lobules and produce large amounts of keratin. Some of this keratin form epithelial or squamous pearls (inset of A)

- **Ipilimumab; Vemurafenib** (signal transduction inhibitors)
- **Oncolytic virus therapy.** (See Fig. 23.5A and B)

SALIVARY GLAND TUMORS

Most Commons in salivary gland tumors

- MC salivary gland tumor overall = **pleomorphic adenoma**
- MC malignant salivary gland tumor = **Mucoepidermoid carcinoma**
- MC parotid gland tumor = **pleomorphic adenoma**
- MC site of salivary gland tumor = **parotid (70%)**
- MC site of Malignant salivary gland tumor = **minor salivary glands** > sublingual gland > submandibular gland > parotid glands (malignancy is inversely proportional to the size of the gland).
- MC salivary gland tumor in **minor salivary glands** = **Adenoid cystic carcinoma (MC in palate).**



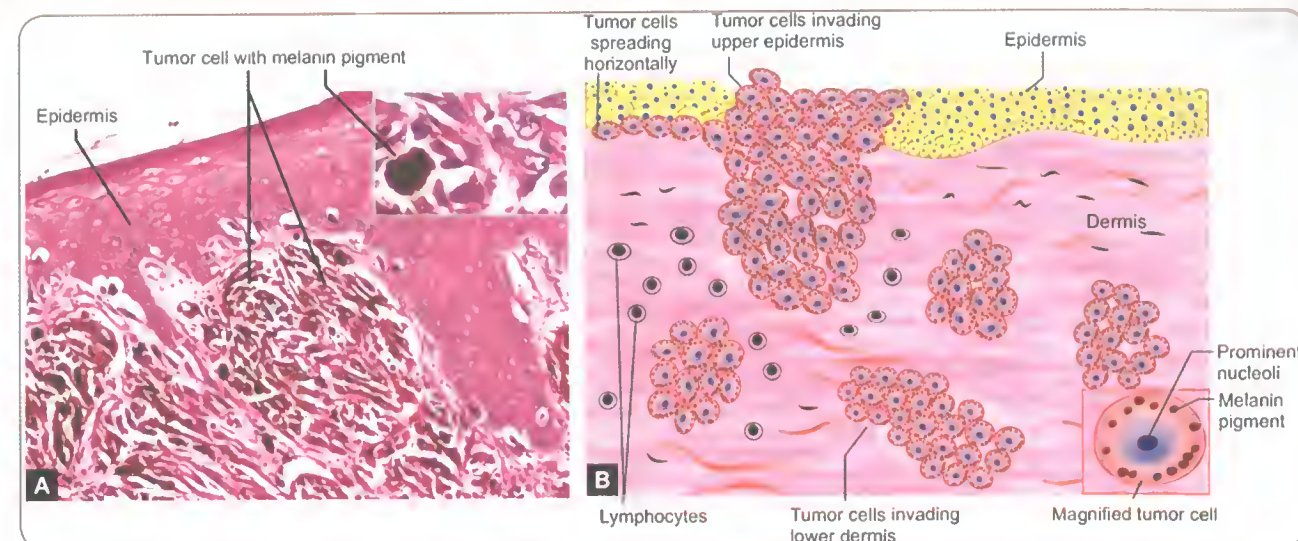
Fig. 23.5: Typical parotid tumor—a pleomorphic adenoma

OCULAR TUMORS

Malignant Melanoma of Choroid (Choroidal Melanoma)

- Clinically
 - MC Primary intraocular tumor in adults.
 - Age: 50–60 years, **mushroom shaped mass** on B scan, metastases MC to liver.
 - Elevated subretinal oval brown/black mass with orange pigment (**lipofuscin**) on surface of tumor
 - Secondary **exudative RD**, choroidal hemorrhage, vitreous hemorrhage (**Knapp-Ronne type**), secondary glaucoma, cataract, uveitis, **vortex vein invasion**.
- Pathology
 - **Spindle A and B, epithelioid, mixed cell types - Callenders classification**; Armed Forces Institute of Pathology (modified Callender's classification).

- **Warthin's tumor (adenolymphoma)** – benign – almost fully limited to parotid gland only; MC in smokers; produces 'hot spot' in 99mTC scan.
- **Adenoid cystic carcinomas** has tendency to invade perineural spaces.
- Clinical features of malignant salivary tumors:
 - Facial nerve weakness
 - Rapid enlargement of swelling
 - Induration and/or ulceration of overlying skin
 - Cervical node enlargement
- Three cranial nerves are at risk during removal of the submandibular gland:
 - Marginal mandibular branch of facial nerve
 - Lingual nerve
 - Hypoglossal nerve.



Figs. 23.6A and B: A. Photomicrograph of malignant melanoma showing nests of tumor cells in the upper dermis containing melanin pigment. Inset shows tumor cell with melanin pigment; B. Diagrammatic microscopic appearance of malignant melanoma showing nests of tumor cells infiltrating epidermis (radial growth phase) and dermis (vertical growth phase)

- **Zimmerman hypothesis:** Early peak in mortality due to increased metastases after enucleation in the first 2 years of treatment.
- Treatment
 - **Enucleation** for large tumors; for medium to small tumors laser photocoagulation with plaque radiotherapy (**brachytherapy**).

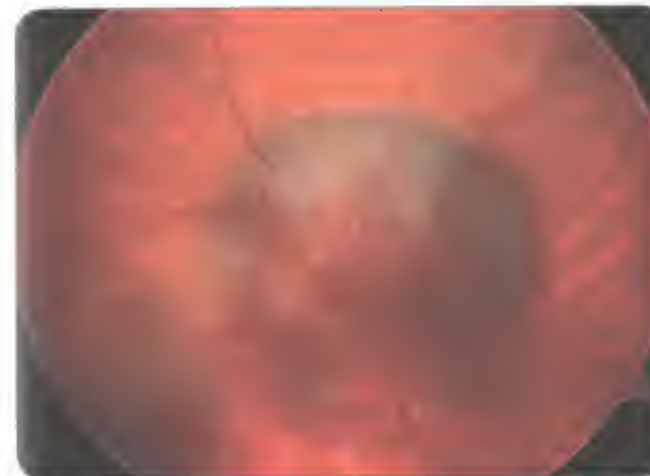


Fig. 23.7: Choroidal melanoma

Retinoblastoma (RB)

- MC primary intraocular tumor of childhood; presents in 1–2 years age group; one of the most curable neoplasm's affecting children with cure rates > 90%!

Genetics of retinoblastoma

- **RB1 gene** is a tumor suppressor gene located on **13q14** (13 associated with bad luck!).
- **Knudson's 2-hit hypothesis** – both alleles must be knocked out for tumor to develop.
- **Sporadic/non-hereditary cases** = usually unilateral (MC, about 75%).
- **Hereditary cases: Autosomal dominant; bilateral;** A/w MC second tumor in RB patients is **osteogenic sarcoma**; **Trilateral RB** = bilateral RB + **pinealoblastoma**

- Pathologically
 - **Exophytic, endophytic or diffuse infiltrating types.**
 - Flexner-Wintersteiner true Rosette and Fleurettes seen in Retinoblastoma. **Homer Wright pseudorosette** is found in neuroblastoma or medulloblastoma and rarely in RB.
 - **Increased aqueous LDH** with aqueous to serum LDH ratio >1.0 indicates retinoblastoma.
 - Total tumor necrosis → **spontaneous regression**, rare.
- Clinically: **Leukocoria** (white pupillary reflex/cat's eye reflex) is the MC presenting sign, second MC is **strabismus**, others include **glaucoma**, **retinal detachment**, **pseudouveitis with hypopyon** (masquerade syn.), **proptosis**.
- Imaging: B scan and CT scan are useful in detecting **calcifications—pathognomonic**; B scan shows 'cauliflower' like mass.
- Treatment: Options:

- Photocoagulation
- Cryotherapy
- Plaque radiotherapy (Brachytherapy)
- Chemotherapy
- Enucleation.

Indications for enucleation

- Unilateral RB that completely fills the globe or has disrupted the retina and vitreous so extensively that restoration of vision is not possible.
 - Bilateral RB where restoration of vision is thought to be not possible
 - Tumor in the anterior chamber
 - Painful glaucoma with loss of vision after rubeosis
- For limited unilateral or limited bilateral disease: all the above may be needed/tried except enucleation.
 - For Bilateral disease: **chemotherapy** to reduce size of tumor and increase likelihood of globe salvage; also to decrease risk of pinealoblastoma. (carboplatin, cyclophosphamide and
 - For Advanced unilateral disease: Enucleation
 - ★ **Note:** During enucleation DO NOT perforate the globe and **excise the longest possible segment of optic nerve** in continuity with the globe.
 - **Reese Ellworth classification** of RB relates to visual prognosis – to predict which eyes were likely to retain vision following radiotherapy.
 - **MC route of spread** of retinoblastoma is through the **optic nerve**.



Fig. 23.8: Leukocoria—retinoblastoma—RE

D/D of Leukocoria or White Pupillary Reflex

- Coat's disease
- Choroidal coloboma (Large)
- Congenital cataract
- Congenital retinal schisis
- Incontinentia pigmenti
- High myopia with advanced chorioretinal degeneration
- Juvenile xanthogranuloma
- Norrie disease
- Organization of Intraocular hemorrhage
- Persistent hyperplastic primary vitreous.
- Toxocara endophthalmitis.
- Uveitis from toxoplasma, CMV, Herpes
- Retinal Dysplasia.
- Retinal detachment
- **Retinoblastoma**
- Retinopathy of prematurity
- Retrolental fibroplasias

EXTRA EDGE

- **Retinoblastoma** was initially **misnamed as glioma** (thought to arise from glial cells); all other conditions causing leukocoria were labeled as **pseudoglioma**.

Rhabdomyosarcoma (Embryonal Sarcoma)

- Arises from **undifferentiated mesenchymal cell rests** which have the potential to differentiate into striated muscle and NOT from striated muscle.
- Histopathologic types: **Embryonal (MC type)**, alveolar, pleomorphic, and botryoid
- Presents **within 7 years** with **rapidly progressive unilateral proptosis** which may mimic inflammatory process.
- **MC superonasally** or retrobulbar; swelling is present but skin is **NOT warm**.
- Treatment is **multimodal** with **radiotherapy, surgery and chemo therapy**.
- Tumors localized to orbit have a **95% cure rate**.
- Prognosis of rhabdomyosarcoma is poor in extremities.

Most commons in eye tumors

- MC primary intraocular Tumor in children – **retinoblastoma**
- MC primary intraocular Tumor in adults – **malignant melanoma**
- **MC benign orbital Tumor in adults: Cavernous hemangioma**
- MC malignant orbital Tumor in children – **rhabdomyosarcoma (embryonal sarcoma)**
- MC Tumor which metastasizes to eye – **neuroblastoma** (in children)

Other Orbital Tumors and Disorders

Capillary Hemangioma

- **MC benign orbital tumor in children**
- Appears in **first month after birth**, **> 90% disappear spontaneously by age of 7**; **strawberry birthmark** – superficially on skin – only observation required
- Eyelid and orbital hemangiomas may cause visual problems and amblyopia – treatment required and includes intralesional corticosteroid, pulsed dye lasers, surgery.
- Beta blocker used for involution of eyelid capillary hemangioma: Oral **PROPRANOLOL**!

Cavernous Hemangioma

- **MC benign orbital tumor in adults**; seen as retrobulbar mass within muscle cone (**intraconal**), **well circumscribed**, **NO bony erosion**; causes **slowly progressive proptosis** (rapid in pregnancy), hyperopic shift, choroidal folds, increased IOP, Optic Nerve compression.
- **Complete excision** by orbitotomy possible due to thick capsule.

Orbital Cellulitis

- **MC cause is ethmoidal sinusitis** which Extends into the orbit through the **medial wall (lamina papyracea)**, **the thinnest wall of the orbit**.
- Ophthalmic emergency; requires admission, close monitoring and systemic antibiotics.

Optic nerve glioma

- **Slow growing pilocytic astrocytoma**; 30% have **NF1** (these have better prognosis); affects **children < 10 years**
- **Gradual visual loss** and **painless axial proptosis** occurs **later**, optic disc edema and later optic atrophy; **Enlargement of optic foramen** on CT; fusiform enlargement of optic nerve
- Treatment: NO treatment if no growth of tumor and vision good; surgical excision for proptosis

Optic Nerve Sheath Meningioma

- Arise from meningotheial cells of arachnoid villi surrounding the optic nerve.
- Triad of
 - **Pale swollen optic disc** – **optic atrophy**, and
 - **Long standing visual impairment**
 - **Optociliary shunt** vessels
- **CT scan shows thickening and calcification of optic nerve**
- **Gaze evoked amaurosis pathognomonic**.
- Treatment: surgical excision followed by radiotherapy.

Orbital Varices

- These are weakened segments of orbital venous system; phleboliths may be present; early childhood to middle age affected
- MC unilateral; MC upper nasal; **intermittent NON-pulsatile proptosis NOT a/w bruit**
- Rapidly reversible **proptosis may be precipitated by Valsalva**, cough, straining, assuming dependent position
 - **USG/MRI scan** needed.

Carotidocavernous Fistula

- A communication between carotid artery (ICA) and cavernous sinus (AV fistula)
- **'Direct' fistula**: defect in wall of intracavernous portion of ICA; **MC cause is trauma**, **high-flow** shunt; **classical triad of conjunctival chemosis, pulsatile proptosis** and a **whooshing noise in the head**; severe episcleral congestion (**corkscrew conjunctival vessels**) with raised IOP; anterior segment ischemia and ophthalmoplegia may be seen.
- CT and MRI demonstrate **prominence of superior ophthalmic vein**. **MR angiography** is the investigation of choice.
- **'Indirect' fistula**: arterial blood flows thro **meningeal branches of ICA or ECA to cavernous sinus**, **'dural slow shunt'**; clinical signs are more subtle
- Treatment: Best choice is **intravascular embolisation** with coils or balloons.

Lymphangioma Orbit

- <20 years of life; slowly progressive **proptosis that is intermittent** and maybe exacerbated by upper respiratory infections; MRI is diagnostic; CT shows nonencapsulated irregular mass (**crabgrass in orbit**)

Childhood metastatic tumors in orbit

- **Neuroblastoma (MC)** – presents with **bilateral abrupt proptosis** with lid swelling/ecchymoses
- **Myeloid sarcoma (granulocytic sarcoma**; earlier called **'chloroma'** due to green color)—**rapid proptosis** in child; uni/bi lateral
- **Langerhans cell histiocytosis**—uni/bi lateral **osteolytic** lesions in superotemporal quadrant

Adult metastatic tumors in orbit

- Rare cause of proptosis in adults; MC due to **breast Ca metastases**

TUMOR LYSIS SYNDROME

- It is caused by destruction of large number of rapidly proliferating neoplastic cells.
- A/w *Burkitt's lymphoma, ALL, CLL*.

Features of tumor lysis syndrome

- Hyperuricemia
- Hyperkalemia
- Hyperphosphatemia
- *Hypocalcemia*
- Lactic acidosis

EXTRA EDGE

- For prevention of tumor lysis syndrome: Adequate *hydration and allopurinol* is used.
- For treatment: *Rasburicase* is used (AVOID in G-6-PD deficiency)
- Systemic bicarbonate to alkalinise the urine is *NO* longer used.

LACRIMAL GLAND TUMORS

- *Pleomorphic adenoma* (benign mixed tumor) is the *MC tumor* of the lacrimal gland. (It is also the *MC benign tumor* of lacrimal gland)
- *Adenoid cystic carcinoma* is the *MC malignant tumor* of the lacrimal gland.
- Classically lacrimal gland tumors cause a '*down and in*' type of proptosis.
- Treatment is mainly *surgical*.

Note

The following cancers have been dealt with under their respective specialty:

- For Gynecologic cancers — see Gynecology chapter
- For Bone cancers — see Orthopedics chapter
- For Breast, Thyroid and Oral cancer — see Surgery chapter

CHAPTER**24****Obstetrics****Author's Note**

- Oogenesis, spermatogenesis, fertilization and related matter have been covered under Embryology chapter (Pg 1).
- Female Reproductive Anatomy and Menstrual Physiology have been covered under Gynecology Chapter (Pg 997).

PLACENTA AND FETAL MEMBRANES**Decidua**

- *Decidua* is the endometrium of the pregnant uterus.
- *Decidual reaction*: The increased structural and secretory activity of the endometrium that is brought about in response to *progesterone* following implantation is known as decidual reaction.
- The well-developed decidua differentiates into three layers:
 1. Superficial compact layer.
 2. Intermediate spongy layer (*decidua spongiosa*)—it is through this layer that *cleavage of placental separation* occurs.
 3. Thin basal layer—*regeneration of mucosa* occurs from this layer following parturition.
- After *interstitial implantation* of the blastocyst into the superficial compact layer of the deciduas, the different portions of the deciduas are renamed as follows:
 1. *Decidua basalis* or *serotina*—the portion of deciduas in contact with the base of the blastocyst.
 2. *Decidua capsularis* or *reflexa*—the thin superficial compact layer covering the ovum.
 3. *Decidua vera* or *parietalis*—the rest of the deciduas lining the uterine cavity outside the site of implantation.
- At term, the decidua vera and capsularis become *atrophied* due to pressure and the two cannot be defined a double layer.
- The *decidua basalis*, however, retains its characteristic appearance till term and becomes the *maternal portion of the placenta*.

Placenta

- The human placenta is:
 - *Discoid*, because of the shape

- *Hemochorial*, because of direct contact of chorion with maternal blood
- *Deciduate*, because some maternal tissue is shed at parturition.
- The **placental barrier** is 0.025 mm thick and consists of:
 - Syncytiotrophoblast
 - Cytotrophoblast
 - Basement membrane
 - Stromal tissue
 - Endothelium of fetal capillary wall with its basement membrane.
- **Development of placenta**: is from 2 sources: *fetal* component is the *chorion frondosum* (*principal component*) and *maternal* component is the *decidua basalis*.

Important Placental Numericals

- Placenta formation begins at **6th** week and is complete by **12th** week.
- The placenta at term is a circular disc with a diameter of 15–20 cm and thickness of about 2.5 cm at its center.
- It weighs about **500 g**, the proportion to the weight of the baby being roughly **1:6 at term** and occupies about 30% of the uterine wall.
- At term, about **4/5th** of the placenta is of fetal origin.

Placental Circulation

- Volume of blood in *mature placenta* = 500 ml.
- Volume of blood in *intervillous space* = 150 ml
- *Fetal blood flow through the placenta* = 400 ml/min.
- Uteroplacental circulation is established by D12 after fertilization, fetoplacental circulation by D21.

Placental Abnormalities

- **Placenta succenturiata**: One or more *accessory lobes* of placenta may be placed at varying distances from placental margin. A leash of vessels connecting the main to the small lobe traverses through the membranes. The accessory lobe is developed from the activated villi on the *chorion laeve*. In cases of absence of communicating blood vessels, it is called *placenta spuria*.

Placenta extrachorialis: 2 types:

- **Circumvallate placenta:** The fetal surface is divided into a central depressed zone surrounded by a thickened white ring, which is usually incomplete.
- **Placenta marginata:** A thin fibrous margin is present at the margin of the chorionic plate where the fetal vessels appear to terminate.
- **Placenta membranacea:** Unduly **large and thin placenta** so that the whole of the ovum is practically covered by the placenta.
- **Battledore placenta:** The **umbilical cord is attached to the margin** of the placenta (**racket handle** attachment).
- **Velamentous placenta:** **Umbilical cord is attached to the membranes.** The branching vessels traverse between the membranes for a varying distance before they reach and supply the placenta. If the blood vessels happen to traverse through the membranes overlying the internal os, in front of the presenting part, the condition is called **vasa previa** (entirely fetal blood).

EXTRA EDGE

- **Nitabuch's membrane** is the zone of **fibrinoid degeneration** where decidua and syncytiotrophoblast meet. It **limits** further invasion of decidua by the trophoblast - its absence can cause **placenta accreta**.
- **Hoffbauer cells** are macrophages in the stroma of placenta.

HORMONES SECRETED BY PLACENTA

- Main site of hormonal synthesis in placenta: **syncytiotrophoblast**.

Type	Hormones
Protein hormones	Human Chorionic Gonadotropin (hCG) Human Placental Lactogen (HPL) Human chorionic thyrotropin (HCT) Human chorionic corticotropin (HCC) Pregnancy specific β -1 glycoprotein
Steroid hormones	Estrogen
Progesterone	

Human Chorionic Gonadotropin (hCG)

- Synthesized by the **syncytiotrophoblast** of the placenta.
- It is a **glycoprotein** hormone with the **highest carbohydrate content** of any human hormone.
- Half life = **24 hours**; Doubling time = **1.4–2 days**.
- Most sensitive test to detect hCG: Fluorescence Immunoassay (FIA).

Levels of hCG

- hCG be detected in the maternal serum/urine **as early as 8–9 days** following ovulation – used to detect pregnancy.
- **Maximum hCG** levels in blood and urine seen between **60–70 days** of pregnancy (100–200 IU/ml)
- **Minimum hCG** levels (10–20 IU/ml) seen at about **16 weeks** (100–130 days)
- **↑ hCG** levels seen in
 - Multiple pregnancy
 - Hydatidiform mole or choriocarcinoma
 - Down's syndrome fetus
- hCG disappears
 - From **maternal urine** at **48 hours** after delivery
 - From the **maternal circulation** within **2 weeks** following delivery
- Minimum concentration of **hCG** at which **gestational sac** is visible
 - On **transvaginal U/S** = **1500** mIU/mL
 - On **abdominal U/S** = **6000–6500** mIU/mL

Functions of hCG

- hCG **maintains the corpus luteum** (and thus progesterone) for the 1st trimester by **acting like LH** (otherwise no luteal cell stimulation, and abortion results).
- hCG **stimulate Leydig cells** of male fetus to produce **testosterone** in conjunction with fetal pituitary gonadotropins—thus **indirectly involved in development of male external genitalia**.
- hCG has got **immunosuppressant** activity and **prevents rejection** of fetus
- hCG **stimulates** both adrenal and placental **steroidogenesis**
- hCG **stimulates maternal thyroid** because of thyrotropic activity.
- hCG promotes uterine relaxation and uterine vascular dilatation.

Correlation between hCG Levels and TVUS Findings

TVUS finding	Minimum hCG level (mIU/mL) at which visible
Gestational sac	1500
Yolk sac	2500
Fetal pole	5000
Fetal cardiac activity	17,000

Human Placental Lactogen (HPL)

- Aka **human chorionic somatotropin**.
- Can be detected in maternal serum at **3 weeks** of gestation.
- Highest HPL levels: at 34–36 weeks
- Half life = 15–30 minutes.

Functions of HPL

- Increases insulin resistance in mother.
- Promotes maternal lipolysis: levels of FFA are increased which mother utilizes as a source for energy (sparing glucose for the fetus).
- It prepares the breast for lactation.

Estrogen

- Estrogen production **depends upon fetal precursors**, i.e. DHEA-S produced by fetal adrenal glands is utilized by placental enzymes to synthesize estriol and estradiol.
- **Note:** Placenta alone cannot synthesize estrogen due to lack of 17-alpha hydroxylase which converts C21 to C18 steroid.
- **Most specific estrogen** in pregnancy: **Estriol (E3)**.
- Hormone which can be used as a **marker of fetal well being: Estriol (E3)**.

Progesterone

- It is the chief hormone produced by **corpus luteum in initial 6–7 weeks** of pregnancy.
- At **8–10 weeks**, **placenta takes over** the function of corpus luteum.
- Precursors from fetal origin are **not** necessary as in estrogen production.
- Progesterone is majorly responsible for maintaining **myometrial quiescence** during pregnancy.

Low progesterone levels

Ectopic pregnancy
Abortion

High progesterone levels

Hydatidiform mole
Rh isoimmunization

UMBILICAL CORD

- Umbilical cord (or **funicis**) connects the fetal umbilicus and fetal surface of placenta through which fetal blood flows to and from the placenta.
- It develops from the **connecting stalk** and can be regarded as a **fetal membrane**.
- It has **2 arteries** and **1 vein** (**Right umbilical vein disappears**).
- Normal umbilical cord length = about **40 cm** (30–100 cm).
- Usually cord is cut **2.5 inches or 6 cm** from the umbilical base.
- The umbilical arteries DO NOT possess an internal elastic lamina but have got **well developed muscular coat**. These **help in effective closure** of the arteries due to **reflex vasospasm** soon after birth of the baby.
- Both the arteries and vein DO NOT possess vasa vasorum.

- In their normally distended state, the umbilical arteries exhibit transverse **intimal folds of Hoboken**.
- **Wharton's jelly** in umbilical cord is rich in mucopolysaccharides and has got protective function to umbilical vessels.

EXTRA EDGE

- **Single umbilical artery**
 - Absence of the **left** umbilical artery is **MC** ('Left gets Left off!').
 - Is often a/w fetal congenital anomalies [genitourinary anomalies (MC), CVS anomalies, GIT obstructive anomalies and trisomy 18].
- **Umbilical coiling index (UCI)**
 - UCI is seen on **ultrasound** refers to number of coils/cm of umbilical cord.
 - **Normal** coiling index = **0.17** coils/cm.
 - **Hypocoiling** (< 0.07) is a/w **fetal death**.
 - **Hypercoiling** (> 0.3) is a/w **IUGR** and fetal acidosis.

FETAL MEMBRANES

- **Outer chorion:** represents remnant of chorion leavae and ends at margin of placenta. It is formed **8 days** after fertilization. **Chorion frondosum** forms **placental villi**. Chorion leavae gets merged with amnion.
- **Inner amnion:** **thinner** than chorion. It is formed **between 10–11 days** after fertilization. It has got **NO** nerve supply, **NO** blood supply and **NO** lymphatic system. It can be peeled off from the fetal surface of the placenta **except** at the umbilical cord.

AMNIOTIC FLUID

- Production: from **mixed maternal and fetal** origin.
- Circulation: Amniotic fluid contains **99% water**. This water in the amniotic fluid is **completely changed and replaced every 3 hours**.
- It is colorless, but becomes pale straw colored at term.
- Chemistry: Fluid is faintly **alkaline (pH 7.2)** with a **low specific gravity** of 1.010. It is **hypotonic**. An osmolarity of **250 mOsm/l** is suggestive of **fetal maturity**.
- Volume: **Maximum of 1 L** at **36–38 weeks**. At **term** it is **600–800 mL**.

Abnormal colors of Amniotic Fluid

- **Meconium stained (green):** Is suggestive of **fetal distress** in presentations other than transverse or breech
- **Golden** color: in **Rh incompatibility** (due to excessive hemolysis)
- Greenish yellow (**saffron**): In **postmaturity**
- **Dark brown (tobacco juice):** In **Intrauterine death** (dark, due to presence of old HbA)
- **Dark colored:** In **concealed accidental hemorrhage** (due to contamination of blood).

Functions of Amniotic Fluid

- During pregnancy:
 - Acts as **shock absorber** and protects the fetus
 - Maintains even **temperature**
 - It distends the amniotic sac and thereby allows for growth and free movements of the fetus and prevents adhesion between fetal parts and amniotic sac.
 - Amniotic fluid has **NO** role in nutrition.
- During labor:
 - Helps in **dilatation of cervix** (due to hydrostatic wedge action of amnion and chorion combined together)
 - Guards against **umbilical cord compression**.

Oligohydramnios vs Polyhydramnios

	Oligohydramnios	Polyhydramnios
Amniotic fluid volume	< 200 ml at term	> 2 Liters
Etiology	<ul style="list-style-type: none">• Drugs (PG inhibitors, ACE inhibitors)• Fetal renal conditions (Renal agenesis; obstructive uropathy; prune belly syndrome; bilateral multicystic dysplastic kidneys)• Premature rupture of membranes (PROM)• Postmaturity• Anion nodosum• Chromosomal anomalies• IUGR• Maternal HTN	<ul style="list-style-type: none">• Excess liquor amni (anencephaly, open spina bifida)• Fetal swallowing difficulty (cleft lip and palate; esophageal and duodenal atresia)• Aneuploidy• Chorioangioma of placenta• Hydrops fetalis• Multiple pregnancy (polyhydramnios is MC in monozygotic twins, usually affecting the second sac)• Idiopathic
Clinical Features	<ul style="list-style-type: none">• Uterus smaller than period of amenorrhea• Less fetal movements• Uterus is 'full of fetus'• Malpresentation (breech) is common• A/w IUGR of fetus	<ul style="list-style-type: none">• Dyspnea; palpitation; edema of legs; varicosities in vulva or hemorrhoids• Enlarged abdomen with shiny skin and striae• Height of uterus > period of amenorrhea• Fluid thrill present all over the uterus.• Fetal parts cannot be well defined.• External ballotment can be elicited easily.
AFI on U/S	< 5 cm	> 25 cm
SDVP on U/S	< 2 cm	> 8 cm
Complications	Mainly fetal : <ul style="list-style-type: none">• Cord compression → fetal hypoxia• IUGR• Pulmonary hypoplasia• Clubfoot• Potter's facies (low set ears, epicanthic folds, receding mandible and flattened nose)	<ul style="list-style-type: none">• Pre-eclampsia (25%)• Preterm labor• Abruptio placentae• Fetal malposition• Cord prolapse

EXTRA EDGE

- **Chronic** polyhydramnios is **10 times more common** than the acute one.
- **Amnio-infusion** is the technique to increase intrauterine fluid volume by infusing warm saline (37°C).
- **Serial amniocentesis** is the **treatment of choice for polyhydramnios** for patient in distress (fluid removed is 500 ml/hour upto maximum of 1.5–2 L).

Assessment of Amniotic Fluid

- **Amniotic Fluid Index (AFI)**: Sum of the largest vertical pocket of amniotic fluid in four quadrants of the uterus.
 - Normal AFI = 5–25 cm.
 - AFI < 5 cm = **Oligohydramnios**.
 - AFI > 25 cm = **Polyhydramnios**.
- **Single Deepest Vertical Pocket (SDVP)** of amniotic fluid.
 - Normal range = 2–8 cm.
 - > 8 cm = Polyhydramnios (mild = 8–11 cm; moderate = 12–15 cm, severe > 16 cm)
 - < 2 cm = Oligohydramnios.

Amniotic Fluid Indicators/Tests of Fetal Lung Maturity

- Fetal lung maturity assessment is necessary since preterm infants with immature lungs are at high risk for respiratory distress syndrome (RDS) which results from lack of surfactant necessary for lung expansion.
- DM complicated pregnancies also exhibit delayed fetal pulmonary maturity.

- Prevented by giving **antenatal glucocorticoids**—dosage given under RDS in Pediatrics chapter (Pg 667).

Physical

- Osmolarity of 250 mOsm/liter
- **Shoke** test or **Foam** test or **Bubble test (Clements)**: based on the ability of pulmonary surfactant to form a bubble or foam on shaking which remains stable for at least 15 minutes. An index of >0.47 on shake test indicates enough fetal lung surfactant and this indicates fetal lung maturity.

Cytological

- **Orange** colored cells > 50% when stained with 0.1% Nile blue sulfate

Chemical

- Lecithin: Sphingomyelin ratio > 2; **L:S ratio is gold standard test**
- Identification of **phosphatidyl glycerol**
- Creatinine > 2 mg/100 ml

Spectrophotometric (Non-immunized mother)

- **Optical density difference** at 650 nm > 0.15; Optical density difference of amniotic fluid occurs due to presence of 'lamellar bodies' (which store surfactant and are secreted by fetal type II pneumocytes after 20 weeks of gestation).

EXTRA EDGE

- **L:S ratio** maybe **falsely high** in **diabetics**; hence presence of **phosphatidyl glycerol** is considered as gold standard test in diabetic women.
- More recently the **lamellar body count** in the amniotic fluid (>35,000/microliter indicates fetal lung maturity) has been shown to correlate well with L:S ratio—it can be performed more quickly, easily, is less expensive and requires a minimum amount of amniotic fluid (BUT still most recent textbooks mention L:S ratio as the gold standard test!).
- Another test is 'Microviscosity Fluorescence Polarization Assay' (detects surfactant: albumin ratio).

FETAL BLOOD

Fetal Hematopoiesis

Structure	Period of hematopoiesis
Yolk Sac (1st site)	16th day to 8 weeks
Aorta-Gonad-mesonephros (AGM)	Day 23 to 40 (from ventral aspect of the aorta in periumbilical region)
Liver	5 weeks-to term (peak period is 6–18 weeks)
Bone Marrow	8 weeks onwards - Term and adulthood (fully established by 28–30 weeks)

- Fetal RBCs are **bigger in size** and **lifespan of fetal RBCs** is two-third that of adult RBCs, i.e. **80 days**.
- **WBCs appear** after **2 months** of gestation.

- During first half of pregnancy, hemoglobin is of fetal type **HbF** (α2, γ2); but **24th week onwards** adult type of **Hb** (α2, β2) appears.

At term

- Total Hb = **16–18 g/dL**
- Fetal Hb (**HbF**) = **75–80%**
- Adult Hb (**HbA**) = 20%
- Between 6–12 months after birth, HbF is replaced by HbA.
- Maternal **IgG crosses placenta from 12th week** onwards and at term fetal IgG is 10% greater than maternal IgG.
- **Urine** production is about **650 ml/day**.

LANDMARKS IN FETAL DEVELOPMENT

Event	Time of Occurrence
Genital ridge formed by	5 weeks
Testis develops by	7 weeks
Ovary develops by	8 weeks
Internal genitalia	10 weeks
Gender (sex) of fetus can be identified on U/S by	14 weeks
Gross body movements	8 weeks
Fetal breathing movements	11 weeks
Urine production begins by	12 weeks
Insulin synthesis	12 weeks
Meconium passage by	16 weeks
Stratum corneum develops after	21 weeks
Scoring movements by	24 weeks
Fetus can hear by	24 weeks
Light perception by	28 weeks

PHYSIOLOGY OF FETAL CIRCULATION

- This has been discussed under **CVS in pediatrics chapter** since it is necessary for understanding congenital heart diseases.

PHYSIOLOGIC RESPONSE OF MOTHER TO PREGNANCY

Weight Gain during Pregnancy

I. Reproductive weight gain: 6 kg	II. Net maternal weight gain: 6 kg
<ul style="list-style-type: none">• Fetus—3.3 kg, placenta—0.6 kg• Uterus—0.9 kg and breasts—0.4 kg• Accumulation of fat (mainly) and protein—3.5 kg	<ul style="list-style-type: none">• Increase in blood volume—1.3 kg• Increase in extracellular fluid—1.2 kg

Hematological Changes

Increased in Pregnancy	Decreased in pregnancy
<ul style="list-style-type: none">↑ Blood volume (30–40%; maximum reached at 30–34 weeks)Plasma volume (40–50%)↑ RBC volume (20–30%), Increase in RBC volume is less in comparison to plasma volume-leading to hemodilution in pregnancy↑ Hb mass (in grams, since RBC volume increases)↑ Oxygen carrying capacity of blood↑ WBC count (neutrophil leukocytosis)↑ Serum fibrinogen (by 50%)↑ ESR (4 times)↑ Serum transferrin and TIBC (total iron binding capacity)↑ Levels of all clotting factors except XI and XIII are increased <p>Note: Clotting time and bleeding time are NOT affected</p> <ul style="list-style-type: none">↑ Total plasma proteins (A:G ratio of 1.7:1 decreases to 1:1)	<ul style="list-style-type: none">↓ Hematocrit↓ Packed cell volume↓ Viscosity of blood↓ Hb concentration (i.e. g/dL) since increase in plasma volume is more↓ Platelet count (gestational thrombocytopenia)

Cardiovascular Changes

Increased in pregnancy	Decreased in pregnancy
<ul style="list-style-type: none">↑ Cardiac output = Heart rate x Stroke volume (all are increased).Regarding cardiac output:<ul style="list-style-type: none">– Peak at about 30–34 week– Lowest in the sitting or supine position– Highest in the right/left lateral or knee chest position– Returns to prelabor values by 1 hour following delivery– Returns to the pre-pregnancy level by 4 weeks time	<ul style="list-style-type: none">↓ Peripheral vascular resistance decreases.↓ Maternal BP decreases (BP = CO x PVR); Decrease in diastolic BP > systolic BP. <p>Note: CVP, Mean arterial pressure and pulmonary capillary wedge pressure are unaffected</p>

Clinical CVS changes in Pregnancy

- Heart is pushed upward and outward. Apex beat is shifted to fourth intercostal space about 2.5 cm outside the midclavicular line.
- Pulse rate** increases by **10–15** beats per minute.
- Systolic murmur** in apical or pulmonary area.
- ‘Mammary murmur’**: a continuous hissing murmur over tricuspid area (due to increased blood flow through internal mammary vessels).
- S3 and S4 maybe heard.
- ECHO: increase in left atrial and ventricular diameters.
- ECG: **Left axis** deviation.

EXTRA EDGE

- Supine hypotension** syndrome, **Mengert’s** syndrome: Compression of **inferior vena cava** in **supine** position → decreased venous return, cardiac output and BP (hence pregnant women are advised not to lie supine in late second and third trimester).

Respiratory System

Increased in pregnancy	Decreased in pregnancy
<ul style="list-style-type: none">↑ Tidal volume (by 40%)↑ Minute ventilation↑ Inspiratory capacity↑ Oxygen consumption	<ul style="list-style-type: none">↓ Residual volume↓ Total lung capacity <p>Note: Respiratory rate, Vital capacity, inspiratory reserve volume are unaffected</p>

Renal System

Increased in pregnancy	Decreased in pregnancy
<ul style="list-style-type: none">↑ Renal plasma flow (by 50%)↑ GFR (by 50%)	<ul style="list-style-type: none">↓ Serum creatinine, BUN and uric acid (due to increased GFR)

- Ureter becomes **atonic** (due to high progesterone).
- The dextrorotated ureter presses against the right ureter causing **urinary stasis** (maximum between **24–28 weeks**) - may lead to **hydroureter** and **hydronephrosis**.
- Increased **frequency of urination** noted between 6–8 weeks pregnancy and subsides after 12 weeks. Again reappears in late pregnancy.

Metabolic Changes

- Positive nitrogen balance** is present throughout pregnancy.

- Insulin secretion is increased with increased plasma insulin level. Overall effect is **maternal fasting hypoglycemia** and postprandial hyperglycemia and **hyperinsulinemia**.
- LDL and triglycerides increase** by 40–50% BUT hyperlipidemia of normal pregnancy is NOT atherogenic. HDL increases by 15%.
- Total iron requirement in pregnancy is **1000 mg**.
- Pituitary gland enlarges by 135%** during pregnancy due to estrogen stimulation.

Other Changes

- Pregnancy is a state of **respiratory alkalosis**.
- Raised alkaline phosphatase** occurs (other liver parameters are normal).
- Median nerve compression (**carpal tunnel syndrome**) and **lateral cutaneous nerve** of thigh compression may occur in pregnancy.

Changes in Genital Organs during Pregnancy

Vagina

- Jacquemier’s** sign (described further below in table)
- Increased pH of vagina (**acidic** - prevents pathogens)
- Cytology shows increased **navicular cells** in clusters and increased lactobacilli.

Uterus

- Hypertrophy** and **hyperplasia** of uterus occurs.
- Weight of pregnant uterus at term is **1000 gram** and measures **35 cm** in length (Non-pregant uterus = 70 gram and 7.5 cm!).
- Uterine **fundus enlarges** > uterine body.
- There is **dextrorotation of uterus** and levorotation of cervix.

Braxton Hick’s Contractions

- From early weeks of pregnancy uterus undergoes **spontaneous** contractions.
- These are **infrequent, spasmodic and painless** without any effect on cervical dilatation.
- Patient is **NOT** aware of these contractions.

Sign	Seen at	Features
Goodell’s sign	6th week	Softening of the cervix and bluish discoloration of cervix Also seen in OCP users
Jacquemier’s or Chadwick’s sign	8th week	Dusky hue of the vestibule and anterior vaginal wall due to vascular congestion Also seen in pelvic tumors like fibroid
Osiander’s sign	8th week	Increased pulsation felt through the lateral fornices Also seen in acute PID

- Intrauterine pressure remains **below 8 mm Hg**.
- It ultimately merges with painful uterine contractions during labor.
- It is **NOT** felt in abdominal pregnancy.

EXTRA EDGE

- Ferguson’s reflex:** In labor, the nerve supply to the cervix, causes stimulation of uterine contraction when pressure is put on the cervix.

DIAGNOSIS OF PREGNANCY

Useful formulae

- ▶ **Naegele’s formula: For calculation of EDD**
 - Calculation of the expected date of delivery (EDD) is done by adding 9 calendar months and 7 days to the first day of the last period.
 - Example: the patient had her first day of the last menstrual period on 1st January. By adding 9 calendar months, it comes to 1st October and then add 7 days, i.e. 8th October which becomes the EDD.
 - **Note:** The duration of normal pregnancy is 10 lunar months OR 9 calendar months + 7 days OR 280 days OR 40 weeks.
- ▶ **McDonald’s Rule: For calculating gestational age**
 - The height of the fundus is measured with a tape in cm and multiplied by 8. This again is divided by 7 which gives the gestational age in weeks.

Trimesters

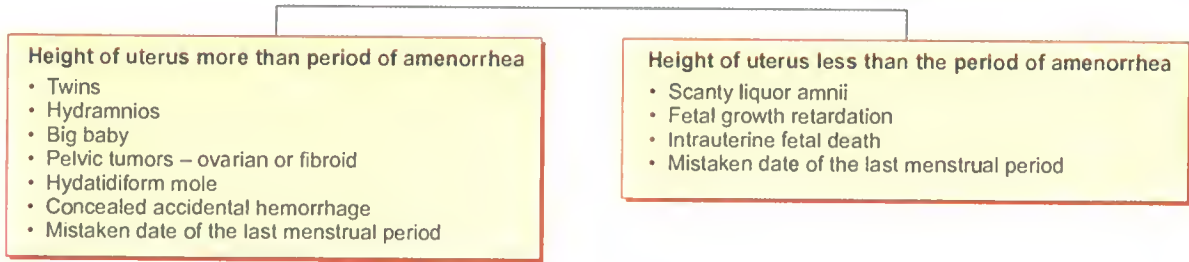
- First trimester = 0–12 weeks
- Second trimester = 13–28 weeks
- Third trimester = 29–40 weeks

First Trimester Features

- Symptoms:** Amenorrhea; Morning sickness; Frequency of micturition; Fatigue; Breast discomfort.
- Signs:** Breast enlargement, engorged visible veins under the skin; nipples and areola more pigmented.
- Internal examination** reveals below signs and ultrasound evidence of gestational ring.

Contd...

Sign	Seen at	Features
Palmer' sign	Between 4–8 weeks	Regular and rhythmic uterine contractions can be elicited during bimanual examination as early as 4–8 weeks
Hegar's sign	Between 6–10 weeks	Principle: (1) upper part of the uterus is enlarged by the growing fetus, (2) lower part of the body is empty and isthmus is extremely soft and (3) the cervix is comparatively firm. Because of the variation in consistency, on bimanual examination. Fingers in the anterior fornix and the abdominal fingers behind the uterus, the abdominal and vaginal fingers seem to oppose below the body of the uterus



Second Trimester Features

- **Symptoms:**
 - Except *amenorrhea*, all the previous symptoms disappear
 - **Quickening** - Perception of active fetal movements (felt at 18 weeks in primigravida and 2 weeks earlier in multipara).
 - Breast changes – *pigmentation of primary areola* and prominence of *Montgomery's* tubercles; *colostrum*; appearance of *secondary areola* at 20 weeks.
 - *Line nigra* and *abdominal striae* maybe seen by 20th week
 - *Chloasma* may appear by 24th week (pigmentation over forehead and cheek).
- **Signs:**
 - Uterus enlarges and becomes an abdominal organ.
 - Flowchart above shows size of uterus corresponding to period of amenorrhea
 - **Braxton Hick's** contractions are evident (discussed above already)
 - **Internal ballotment** can be elicited between 16–28th week
 - **External ballotment** can be elicited by 20th week.
 - Palpation of *fetal parts* can be felt by 20th week
 - **Auscultation of fetal heart sound** is the **most conclusive clinical sign** of pregnancy—detected by stethoscope between 18–20 weeks.

Third Trimester

- **Lightening:** At about 38th week (in primigravidae) a sense of relief maybe obtained due to engagement of presenting part.

- **Frequency** of micturition re-appears
- Fetal movements are more pronounced
- *Braxton Hicks* contractions are more evident.

Absolute (Positive) Signs of Pregnancy

- Palpation of *fetal parts* and perception of *fetal movements* by examiner at about 20th week.
- Auscultation of *fetal heart sounds*.
- U/S evidence of *embryo at 6th* week and later on, the fetus
- *X-ray* evidence of fetal skeletal shadow—earliest by 16th week.

Estimation of Fetal Weight

- **Johnson's** formula: applicable only in vertex presentation
- **Dawn** formula: based on uterine volume using a pelvimeter
- Ultrasonographic formulae:
 - **Hadlock's** formula (*MC* used clinically)
 - **Shepard's** formula
 - **Aoki's** formula

ANTEPARTUM FETAL MONITORING

Non-stress Test (NST)

- In NST, a continuous electronic monitoring of the fetal heart rate along with recording of fetal movements (*cardiotocography*) is noted.
- **Principle:** This test looks for the presence of temporary accelerations of the FHR a/w fetal movement - indicates fetal well being.

- NST testing should **begin at 30 weeks** and is **bi-weekly**.
- A **normal ('reactive')** test is considered to be **2 or more ≥ 15 beat/minute accelerations** over baseline of the FHR that lasts **≥ 15 seconds during a 20 minute** monitoring period.
- A **nonreactive (abnormal) NST** should prompt the performance of a **biophysical profile (BPP)** as below.
- The test has a **false negative rate of 0.5%** and a **false positive rate of 50%**.
- A nonreactive NST can be due to
 - Fetal sleep cycle
 - Gestational age < 30 weeks
 - Fetal CNS anomaly
 - Maternal sedative/narcotic use.

Biophysical Profile (Manning's Score)

- The 5 components measured by real time ultrasound are:
- Fetal Tone
 - Fetal Breathing
 - Fetal Movement
 - Amniotic fluid volume
 - Nonstress test. ('Test the Baby **MAN!**')
- **Indications:** Non-reactive NST; High-risk pregnancy
 - **Test frequency:** weekly once after a normal NST; Twice weekly after an abnormal NST.
 - **Observation time: 30 minutes**
 - **Normal score = 2; Abnormal score = 0; Reassuring score = 8–10; Low score < 6 = fetal distress.**

EXTRA EDGE

- **Modified Biophysical Profile:** NST + Amniotic fluid index (AFI).
- Modified BPP is considered abnormal when NST is non-reactive and/or the AFI is < 5.

Fetal Heart Rate Monitoring

- **Cardiotocography (CTG)** is a technical means of recording the fetal heartbeat and the uterine contractions during pregnancy. The machine used to perform the monitoring is called a cardiotocograph, more commonly known as an **electronic fetal monitor (EFM)**. Two methods of CTG are:
 - **External:** the FHR and the activity of the uterine muscle are detected by two transducers placed on

the mother's abdomen (one above the fetal heart, to monitor heart rate and the other at the fundus of the uterus to measure frequency of contractions). **Doppler ultrasound** provides the information which is recorded on a paper strip known as a cardiotocograph.

- **Internal:** A spiral pointed scalp electrode is placed on the fetal scalp after rupturing the membranes through the cervix.
- Normal FHR = 110–160 beats per minute (bpm) - as per NICHD guidelines.

Fetal bradycardia (<110 bpm) Fetal tachycardia (>160 bpm)

Fetal hypoxia, acidosis Congenital heart block Drugs to mother (pethidine, methyl dopa, propranolol)	Maternal fever due to amnionitis Maternal atropine or terbutaline
--	--

Baseline FHR Variability

- This is the **oscillation of baseline FHR** determined in a 10 minute window excluding the accelerations and decelerations.
- Baseline variability maybe:
 - Absent
 - Minimal (< 5 bpm)
 - Moderate (6–25 bpm)
 - Marked (> 25 bpm)
- Baseline variability of **5–25** denotes a **healthy fetus**.
- **Decreased baseline variability** maybe due to fetal sleep; infections; hypoxia or maternal medications.

Acceleration in FHR

- Acceleration is an **increase in FHR by 15 bpm or more** lasting for at least **15 seconds**.
- Accelerations denote an intact neurohormonal and CVS activity and denotes a **healthy fetus!**
- Absence of accelerations is the **first feature** to denote hypoxia.

Decelerations in FHR

- Decrease in FHR below the baseline by **15 bpm or more** and lasting for **> 15 seconds**.
- Types of decelerations and their causes/significance is given in table.

Type of deceleration	Description	Cause/Treatment
Early decelerations (Type I Dips)	Deceleration begins and ends with uterine contractions	Due to fetal hEAd compression and vagal activation (NO fetal distress) NO treatment required

Contd...

Contd...

Type of deceleration	Description	Cause/Treatment
Late decelerations (Type II Dips)	Deceleration begins after uterine contraction and persist until after the contraction has finished	Indicates fetal hypoxia and chronic uteroplacental insufficiency . If late decelerations are recurrent, immediate delivery is necessary
Variable decelerations	Inconsistent onset, duration and degree of decelerations that disappears with change in position of the patient	Due to umbilical cord compression . Change the mothers position and the decelerations disappears!

EXTRA EDGE

- **Sinusoidal Heart Rate:** It is stable baseline variability without any acceleration. Seen in cases of fetal anemia due to
 - Rh isoimmunization
 - Ruptured vasa previa
 - Twin-twin transfusion

Fetal Scalp Blood Sampling (FSBS)

- If CTG indicates hypoxia, the findings can be corroborated by detecting pH of fetal blood, i.e. **fetal acidosis** reflects **fetal hypoxia**. Hence fetal scalp blood sampling is used.

Scalp blood pH	Interpretation
> 7.25	It is reassuring and monitor labor and repeat pH in 30 minutes
7.21–7.25	Borderline and repeat pH in 30 minutes
< 7.2	Indicates fetal acidosis and do urgent delivery

Vibroacoustic Stimulation Test

- This is done using an electronic larynx placed on maternal abdomen. This changes the fetal sleep state from quiet (non-REM) **to active (REM) sleep**. Presence of FHR accelerations indicates normal blood pH.

Contraction Stress Test

- Aka **Oxytocin challenge test**.
- When there is alteration of FHR in response to oxytocin induced uterine contractions, it indicates fetal hypoxia.
- Used to assess **uteroplacental dysfunction**.

Fetal Movement Count

- The counts should be performed **daily** after **28 weeks** of pregnancy.
 - **Cardiff ‘count -10’ formula:** Patient starts counting fetal movements at 9 AM; counting is stopped as

soon as 10 counts are reached. She has to report to the doctor is

- < 10 movements occur during a 12 hour period on 2 consecutive days
- No movement is perceived even after 12 hours on a single day.

- **Daily fetal movement count (DFMC):** Three counts, each of 1 hour duration in morning noon and night are made. The total count multiplied by 4 gives the 12 hour fetal count. If the number of ‘kicks’ is **< 10 in 12 hours** (or < 3/hour), it indicates **fetal compromise**.

ANTENATAL ULTRASOUND

Important Antenatal Ultrasound Parameters

Crown Rump length (CRL)

- **Best** parameter to assess **gestational age in first trimester** (upto 14 weeks or till CRL is 84 mm).
- Best seen on TransVaginal Ultrasound (TVS).

Biparietal Diameter (BPD)

- **Best** parameter to assess **gestational age between 14–20 weeks**.
- BPD is measured **at the level of** the thalami and cavum septum pellucidum.
- BPD is **measured from** outer edge of the skull on one side to inner edge of the skull on the opposite side.
- **Head circumference** is more reliable than BPD when there is alteration in shape like dolichocephaly, etc.

Femur Length (FL)

- **Best** parameter to assess **gestational age in third trimester** (But gestational age assessment made during third trimester using ultrasound is NOT reliable—variation of ≥ 21 days maybe there!).
- Femoral head is **excluded** in FL.
- Femur can be visualized by **10 weeks** gestational age.

Abdominal Circumference (AC)

- **Best** parameter for assessment of **fetal growth** and **fetal nutrition**.
- Also the **best** parameter to detect **IUGR** and **macrosomia**.
- **AC > 35 mm** indicates **macrosomia**.
- The fetal abdominal circumference is measured on an axial view of the abdomen **at the level of** the **stomach** and **intrahepatic portion of umbilical vein** and **hepatic vein/portal sinus**.

EXTRA EDGE

- **Overall best** parameter and best time to assess gestational age is **CRL and first trimester**.

Gestational Sac on Ultrasound

- The first sign of pregnancy on ultrasound is appearance of **gestational sac**.
- Size of gestational sac is measured by **mean sac diameter** on ultrasound.
- **Definitive diagnosis** of **intrauterine** pregnancy is possible by visualizing the gestational sac as early as **29–35 days** with TVS.

True gestational sac	Pseudogestational sac
<ul style="list-style-type: none">• Eccentric in position within the endometrium of fundus or body of uterus• ‘Double decidua’ sign is seen• Contains yolk sac or fetal pole within it• Size increases by 1.1 mm/day	<ul style="list-style-type: none">• Centrally located in uterus and irregular in outline• No ‘double decidua’ sign• Sac remains empty

EXTRA EDGE

- An intrauterine gestational sac should be seen when the hCG levels are
 - 1500 mIU/mL - on transvaginal U/S
 - 6000–6500 mIU/ml - on abdominal U/S
- **Yolks sac** is seen at hCG level of **7000 mIU/mL** and the **embryo** at **11,000 mIU/mL**.

Gestational age and Embryonic Structures identified by TVS

Gestational Age (weeks)	Fetal structures
5	Gestational sac, embryo, yolk sac
6	Fetal pole, fetal cardiac activity (by 7 weeks on abdominal U/S)
7	Lower limb buds, midgut herniation (physiological)

Contd...

Contd...

Gestational Age (weeks)	Fetal structures
8	Upper limb buds, stomach
9	Spine, choroid plexus

Ultrasound of Anencephaly

- Anencephaly is the **earliest anomaly** to be detected on ultrasound.
- It can be detected earliest by **10 weeks**.
- For best diagnosis of anencephaly, ultrasound should be done at **14 weeks**. Findings are:
 - No calcified cranium
 - Eye of fetus are big - ‘**Frog-eye**’ sign
 - Face shows ‘**Mickey Mouse**’ sign

Ultrasound of Spina Bifida

- Reliably diagnosed with second trimester ultrasound. Signs are.
 - **Lemon** sign: frontal bone scalloping
 - **Banana** sign: Elongation and upward displacement of cerebellum
 - Ventriculomegaly

Maternal Serum Alfa-fetoprotein (MSAFP)

Raised MSAFP Levels

- Fetal causes:
 - **Neural tube defects:** open spina bifida, anencephaly and others
 - GI obstruction, exomphalos and gastroschisis
 - Renal: Nephrosis (polycystic/absent kidney), posterior urethral valve
 - Aplasia cutis, amniotic band disruption
 - IUGR
 - Meckel’s syndrome
 - Osteogenesis imperfecta
 - Placental and umbilical cord tumors, preterm labor
 - Teratoma (sacroccocygeal), Turner’s syndrome (Cystic hygroma), Twins
- Maternal causes:
 - Low maternal weight
 - Underestimated gestational age
 - Maternal diseases like hepatocellular Ca, viral hepatitis and SLE

Low MSAFP Levels

- Down’s syndrome
- Fetal cystic fibrosis
- Fetal hydrocephalus
- ↑ maternal weight
- Overestimated gestational age

Doppler Ultrasonography

- Peak systolic (S), peak diastolic (D) and mean volumes (M) are measured.
- From these values, the *S/D ratio; pulsatility index* {PI = (S-D)/M}; *resistance index* {RI = (S-D)/S} are calculated.
- In a *normal pregnancy*, the SD ratio, PI and RI *decreases*, as the gestational age advances.
- Arterial Doppler (*Umbilical artery*) waveforms help to assess downstream *vascular resistance*.
- Venous Doppler (*ductus venosus, umbilical vein*) provides information about *fetal cardiac function*.
- Doppler changes and their clinical significance is given in below table.

Vessel	Change	Clinical importance
Umbilical artery	Reduced OR absent OR reversed end-diastolic flow	(↑ resistance in fetal circulation) = IUGR; Pre-eclampsia
Middle cerebral artery	↑ diastolic velocity ↓ pulsatility index	'Brain sparing' effect in response to hypoxemia
Ductus venosus and umbilical vein	↑ Doppler index (i.e. ↑ flow resistance)	Fetal acidemia

EXTRA EDGE

- *Serial fetal Middle Cerebral Artery (MCA) Doppler velocimetry* has been used clinically for surveillance for *fetal anemia*.
- On *uterine artery Doppler*, diastolic notch typically disappears by 22 weeks—its persistence is a predictor of *pre-eclampsia*.

DIAMETERS OF FETAL SKULL

Anteroposterior Diameters

Engaging Diameter	Cm	Attitude of head	Presentation
Suboccipito bregmatic	9.5 cm	Complete flexion	Vertex
Suboccipito frontal	10 cm	Incomplete flexion	
Occipito frontal	11.5 cm	Marked deflexion	
Submento bregmatic	9.5 cm	Complete extension	Face
Submento vertical	11.5 cm	Incomplete extension	Face
Mento vertical	14 cm (longest)	Partial extension	Brow

Transverse Diameters

- **Biparietal diameter (9.5 cm)**
 - It extends between the two parietal eminences
 - **Widest** transverse diameter of the fetal skull
 - **Engagement** of the head has taken place when the biparietal diameter has passed through the brim of the pelvis
 - Whatever may be the position of the head this diameter *always engages*.
- **Bimastoid diameter (7.5 cm)**
 - **Narrowest** diameter of the fetal skull
 - **Incompressible**.

EXTRA EDGE

- In *brow presentation* since *mentovertical diameter is engaged* (14 cm!) - always a **Cesarean section must** be done.
- **9.5 cm diameters** in fetal skull are: suboccipito bregmatic, submento bregmatic and bipareital diameters.

MATERNAL PELVIS

- **Angle of inclination:** In the erect posture, the pelvis is tilted forward at an angle of 55 degrees to the horizontal.
- **High inclination** has got obstetric significance—delayed engagement; favors *occipitoposterior* position; difficulty in descent.
- **Low inclination** has NO obstetric significance.
- **Bispinous diameter** is the *narrowest transverse diameter* of the pelvis, **10.5 cm**; lies between the two ischial spines.

Type of pelvis	Comments
Gynecoid (Round)	<ul style="list-style-type: none">• MC type (50%); Aka normal <i>female pelvis</i>• Wide subpubic angle• Normal vaginal delivery possible without any difficulty
Anthropoid (AP oval)	<ul style="list-style-type: none">• Slightly narrow subpubic angle (AP > transverse diameter)• Non-rotation is common• Direct Occipitoposterior position is common• More chances of face-to-pubis delivery
Android (Triangular, Heart shape)	<ul style="list-style-type: none">• Aka Male type pelvis• Narrow subpubic angle• Delayed engagement and difficult anterior rotation• More chances of deep transverse arrest and persistent occipitoposterior position• Difficult instrumental delivery and perineal injuries
Platypelloid (transversely oval - flat bowl like)	<ul style="list-style-type: none">• Least common type (5%)• Very wide (> 90 deg) subpubic angle (Transverse diameter >> AP diameter)• Anterior rotation occurs late

Contd...

Contd...

Type of pelvis	Comments
	<ul style="list-style-type: none">• Head engages with marked asynclitism-engaging diameter is super subporietol (instead of usual BPD)• No difficulty in delivery if head is able to negotiate the asynclitism OR else Cesarean section

Obstetric Significance of the Plane of Least Pelvic Dimension

- **Narrowest** plane in the pelvis.
- Plane roughly corresponds to the origin of levator ani muscles.
- It is at this plane that *internal rotation* of the head occurs.
- It marks the beginning of the forward curve of the pelvic axis.
- It is the *landmark* for *pudendal nerve block analgesia*.
- The *level of ischial spines* indicate **station 'O'**.
- It is irregularly oval and notched on each side by the *ischial spines*.

A-P Diameters of Pelvic Inlet

	True conjugate	Diagonal conjugate (CD)	Obstetric conjugate
Distance from midpoint of sacral promontory to	Upper border of symphysis pubis	Lower border of symphysis pubis	Midline projection of symphysis pubis
Length	11 cm	12 cm	10 cm
Comments	Aka anatomical conjugate; conjugata vera		Shortest AP diameter

EXTRA EDGE

- Obstetric conjugate **cannot** be measured clinically but calculated by subtracting 1.5 from diagonal conjugate, i.e. **DC minus 1.5 cm**. It is the **most important** AP diameter, since it through this that the fetus must pass.
- Similarly **True conjugate = DC minus 1.2 cm**.
- **ONLY** the diagonal conjugate can be assessed during late pregnancy or at time of labor.

Contracted Pelvis

- Anatomically, a pelvis is said to be contracted if any of its major diameters are shortened by 0.5 mm or more.
- Obstetrically, alteration in size and shape of the pelvis of sufficient degree to alter the normal mechanism of labor in an average sized baby.

Types of contracted pelvis

- **Rachitic** pelvis: seen in rickets (triradiate pelvis).
 - **Osteomalacic** pelvis.
 - **Naegle's** pelvis: one ala of sacrum is absent.
 - **Robert's** pelvis: both ala of sacrum are absent.
- In contracted pelvis, mode of delivery is **always Cesarean section** (elective at 38 weeks); it is a recurring cause of Cesarean section.
 - **Thomas dictum:** If sum of bispinous diameter and posterior sagittal diameter of outlet is < 15 cm, then pelvis is said to be contracted and Cesarean section is needed.

Cephalopelvic Disproportion (CPD)

- The disparity between the fetal head and the pelvis (too big head or too small pelvis) is called CPD.
- **Muller-Munro-Kerr** method: *Abdomino-vaginal* bimanual method for diagnosis of CPD (cephalopelvic disproportion) - is better than the abdominal method.
- Best method pelvis/CPD assessment: **MRI > CT > X-rays**.
- In female with mildly *contracted pelvic inlet*—*trial of labor* is tried.
- In female with severe contracted pelvis or pelvis with *outlet or midpelvis contraction*—management of choice is *Cesarean section*.

Trial of Labor

- It is the conduction of spontaneous labor in a moderate degree of CPD in an institution under supervision with watchful expectancy hoping for a vaginal delivery.
- The aim is to avoid unnecessary Cesarean section, BUT if it fails Cesarean section should be done immediately.
- Trial of labor is best for CPD at **level of the inlet**.
- **Contraindications** of trial of labor:
 - Severely contracted pelvis at midpelvis or outlet
 - Previous C-section
 - Elderly primigravida
 - Bad obstetric history
 - Malpresentation
 - Previously failed trial of labor
 - Severe PIH, diabetes or cardiac disease

FETUS IN UTERO

Definitions

- **Lie:** Lie refers to the long axis of the fetus to the long axis of the centralized uterus or maternal spine. **Longitudinal** lie is **MC**.

- **Presentation:** The part of the fetus which occupies the lower pole of the uterus. **Cephalic** is **MC**.
 - **Compound presentation** means prolapse of fetal extremity alongside the presenting part - **MC type is prolapse of hand** in cephalic presentation (i.e. **head + hand**).
- **Presenting part:** Part of the presentation which overlies the internal os. **Vertex** is **MC**.
- **Attitude:** The relation of different parts of the fetus to one another is called attitude—universal attitude is that of **flexion**.
- **Denominator:** An arbitrary fixed point on the presenting part which comes in relation with various parts of the maternal pelvis, e.g. *occiput in vertex; mentum (chin) in face; frontal eminence in brow; sacrum in breech and acromion in shoulder*.

Obstetrical Grips

- A.k.a. **Leopold's maneuvers**
 - Fundus grip
 - Lateral or umbilical grip
 - **Pawlik's grip** (third Leopold) - in transverse lie Pawlik's grip is **empty**.
 - Pelvic grip (fourth Leopold) - examination is done **facing the patient's feet**.



Fig. 24.1: Pawlik's grip or first pelvic grip

Obstetric History Recording Nomenclature

- TPAL system
 - T = Term births (after 37 weeks gestation)
 - P = Premature births (< 37 weeks gestation)
 - A = Abortions
 - L = Living children.
- GTPAL system = Gravidity + TPAL

- GTPALM system = GTPAL + Multiple pregnancies
- GPA system = Gravida, Para, Abortus.

NORMAL LABOR

- Eutocia = Normal labor
- Dystocia = Abnormal labor

Prelabor

- It is the premonitory stage of labor that begins 2-3 weeks before onset of labor in primipara and a few days before in multiparae. It consists of:
- **Lightening:** i.e. decrease in fundal height at term due to formation of lower segment of uterus which allows the presenting part to descend into the pelvis. It brings a **sense of relief** to the mother and is a **welcome sign** as it rules out CPD.
- **Ripening of cervix:** Soft, 80% effaced (<1.5 cm in length); admits one finger easily; is easily dilatable.
- **False labor pains** (see below)

True Labor Pains	False labor Pains
Painful uterine contractions at regular intervals that increase gradually	Dull irregular pains confined to lower abdomen and groin
A/w 'show'; effacement and dilatation of cervix and formation of 'bag of waters'	Not a/w hardening of uterus
NOT relieved by enema or sedatives	Usually relieved by enema and sedatives

EXTRA EDGE

- **Show:** Expulsion of cervical mucus mixed with blood is called 'show'.
- Formation of 'bag of waters' is a **certain sign of labor**.
- **Pain** of uterine contractions is distributed along **T10-L1**.

Normal Labor: Stages and Duration

Stage	Characteristics	Nulligravida	Multigravida
1	Onset of labor to full cervical dilation	12 hrs	6 hrs
2	From full cervical dilation to birth of the baby	2 hrs	30 mins
3	Delivery of baby to delivery of placenta	15 mins	15 mins
4	Placental delivery to hemodynamic stabilization of mother	At least 1 hour	At least 1 hour

Mechanism of Normal Labor

The principal movements in normal labor is:

- Engagement (in all cephalic presentations, the engaging transverse diameter is always **biparietal**)
- Descent
- Flexion (flexion is explained by **two-arm lever** theory)
- Internal rotation {**Most important step** without which further descent would not take place. Internal rotation by law of pelvic floor (**Hart's rule**); Law of unequal flexibility (**Selheim and Moir**)}
- Crowning
- Extension (delivery of the head takes place by extension by '**couple of force theory**')
- Restitution
- External rotation
- Expulsion of the trunk.

EXTRA EDGE

- Cervical dilation is expressed in terms of 'fingers' - 1, 2, 3 or fully dilated OR in terms of cm **10 cm** when **fully dilated**.
- As per **Crichton**, progressive descent of the fetal head can be assessed abdominally by estimating the number of '-fifths' of the head above the pelvic brim (e.g. at 1/5th above, it is a fully engaged head)
- **Ritgen maneuver:** Assisted delivery of the fetal head by extension, exerting and upward pressure to the chin by the right hand placed over the anococcygeal raphe.

Partogram

- Partogram is a composite graphical record of **cervical dilatation** in centimeters and **descent of head** against duration of labor in hours. It also includes the **fetomaternal condition**.
- The concept of partogram was first introduced by **Friedman (1954)**.

How to use the Partogram in Active Labor?

- In a partograph the labor process is divided into:
 - **Latent phase:** from onset of true labor till 4 cm dilation of cervix.
 - **Active phase:** starts with cervical dilation of > 4 cm (as per **WHO partograph**).
- Partogram is **plotted** once the patient enters the active phase (i.e. >= 4 cm cervix dilation)
- Concept of Alert line and Action line given by **Philpott and Castle (1972)**.
 - **Alert line** starts at the end of latent phase (4 cm cervical dilation) and ends with full dilation of the cervix (10 cm) in 7 hours (1 cm/hour dilation rate).

- **Action line** is drawn **four hours to the right** of the alert line.
- As long as the plotted cervical dilatation curve is to the **left** of the alert line (zone 1), it is considered **normal**.
- Labor is considered **abnormal** when cervicograph crosses the alert line and falls on **zone 2**.
- If the curve crosses the alert line and if the patient is in a peripheral hospital, referral to a higher level hospital is necessary.
- **Intervention** is required when it crosses the action line and falls on **zone 3**.

Data recorded in a partogram are

- Patient data - Name, Age, Parity, Hospital identification number, Date of admission, Time of admission, Time of Rupture of membrane
- Dilatation of cervix (cm)
- Station of fetal head ('0' at level of **ischial spines**; If above the spines - it will be -1 cm, -2 cm, -3 cm, -4 cm and -5 cm AND if below the spines - it will be +1 cm, +2 cm, +3 cm, +4 cm and +5 cm). Station at introitus is +5.
- Fetal heart rate
- Number of uterine contractions in 10 minutes
- Moulding (+/++)
- Liquor amni
 - Intact membranes - I
 - Clear liquor - C
 - Meconium staining - M
- Oxytocin units, drops/min
- Drugs (oral and IV fluids)
- Maternal vitals (BP, pulse, temperature, urine for acetone)

INDUCTION OF LABOR

- **Induction of labor** means initiation of uterine contractions (after the period of viability) by any method (medical, surgical or combined) for the purpose of vaginal delivery.
- **Augmentation** of labor is the process of stimulation of uterine contractions that are already present BUT found to be inadequate.

Modified Bishop Score

- This is a quantitative method for prediction of successful vaginal delivery following induction of labor:
 - **Fetal station** (distance of presenting body part above or below ischial spines).
 - Cervical **dilation** (cm)
 - Cervical **length** (cm)
 - Cervical **consistency**
 - Cervical **position**.

- **Note:** In the 'original' Bishop score, cervical 'effacement' was present instead of cervical 'dilation'.

Cervical Ripening

- **Ripening** of cervix refers to changing the cervical matrix from sol to gel state by dissolving the collagen bundles - leading to **softening** of the cervix.
- Techniques for cervical ripening are:

Pharmacological method	Non-pharmacological method
<ul style="list-style-type: none">• Prostaglandin<ul style="list-style-type: none">- Dinoprostone (PGE2)<ul style="list-style-type: none">- Intracervical is 'gold standard'- Misoprostol (PGE1) oral or transvaginal• Steroid receptor antagonist<ul style="list-style-type: none">- Mifepristone- Onapristone• Relaxin• Glyceryltrinitrate, isosorbide mononitrate	<ul style="list-style-type: none">• Stripping the membranes• Amniotomy (artificial rupture of membranes)• Mechanical dilators, osmotic dilators• Transcervical balloon catheter• Extra-amniotic saline infusion

THIRD STAGE OF LABOR

- Third stage is from delivery of baby to delivery of placenta. Average time taken = **15-20 minutes**.
- If it takes > **30 minutes**, it is called **prolonged** third stage.
- With active management of third stage of labor (**AMTSL**), time taken = **5 minutes**.
- Placental separation is along **decidua spongiosum** (intermediate spongy area of decidua basalis).
- Methods of placental separation are: **Schultz** method (**MC, 80%** cases) and **Duncan** method.

Signs of Placental Separation

- Per abdomen:
 - Uterus becomes firmer, globular and ballotable (earliest sign).
 - **Schroeder's** sign: Fundal height is slightly raised as the separated placenta comes down in lower uterine segment and uterus rests over it.
 - **Kustner's** sign: On pushing the uterus cephalad with a hand on the abdomen, the cord no longer recedes.
 - **Suprapubic bulge** maybe seen.
- Per vagina
 - Sudden gush of blood
 - Permanent lengthening of the cord.

Average blood loss during delivery

- In Vaginal delivery: 500 ml
- In Cesarean section: 1000 ml
- In twin vaginal delivery: 1000 ml
- In Cesarean hysterectomy: 1500 ml

Active Management of Third Stage of Labor (AMTSL)

Components of WHO recommendations (2012) for the AMTSL are:

1. The use of **uterotonics** for the prevention of postpartum hemorrhage (PPH) during the third stage of labor is recommended for **ALL** births.
2. **Oxytocin (10 IU, IV/IM)** is the **recommended** uterotonic drug for the prevention of PPH.
3. **Delayed cord clamping:** Delay clamping the cord for **at least 1-3 minutes** to reduce rates of **infant anemia**.
4. Delivery of placenta by **controlled cord traction (CCT)**- **Modified Brandt Andrews** method.
5. **Postpartum vigilance:** Immediately **assess uterine tone** to ensure a contracted uterus; continue to check **every 15 minutes for 2 hours**. If there is uterine atony, perform **fundal massage** and monitor more frequently.

EXTRA EDGE

- **Most important** component of AMTSL is the administration of good quality **uterotonic (oxytocin preferred)** to **every woman** who delivers a baby.

POSTPARTUM HEMORRHAGE (PPH)

- Quantitative definition: Blood loss in **excess of 500 ml** after birth of baby (WHO) OR a drop in **hematocrit of 10%** (ACOG).
- Clinical definition: Any amount of bleeding from or into the genital tract following birth of the baby leading to signs of **hypovolemia** (rising pulse, falling BP).
- MC cause of **maternal mortality in India** is obstetric hemorrhage (**PPH**).
- **Primary PPH:**
 - Occurs **within 24** hours after birth of baby; MC occurs **within first 2 hours**
 - MC occurs **after** expulsion of placenta (TRUE PPH)
 - Bleeding occurring before expulsion of placenta is '**third stage hemorrhage**'.
 - **MC cause** of primary PPH is **atonic uterus**. Other causes are trauma, retained tissues and blood coagulopathy.

- Secondary PPH: occurs **beyond 24 hours** and within puerperium (**6-12 months**). **MC cause** is **retained placental bits**.
- In **atonic PPH**, uterus is flabby and becomes hard on massaging.
- In **traumatic PPH**, uterus is found well contracted.

Diagnosis of PPH

Shock Index

- Shock index = Heart rate/Systolic BP
- This is used in ICU to estimate amount of blood loss
- Normal value = 0.5-0.7
- If value > 0.9-1.1, intensive resuscitation maybe required.

Modified Shock Index (MSI)

- MSI is the ratio of **heart rate to mean blood pressure** (MAP).
- $MAP = \{DBP \times 2 + SBP\} \div 3$

Obstetric Shock index (OSI)

- During pregnancy normal value = 0.7-0.8.
- OSI > 1 indicates massive hemorrhage and need for blood transfusion.

Management of Atonic PPH

Medical Management

- Uterotonic drugs are given to increase the tone of the uterus in atonic PPH.

Uterotonic Drug	Dose	Comment
Oxytocin (Drug of choice)	Drips of 10-20 units in 500 mL normal saline (40-60 drops/minute)	Never give IV bolus of oxytocin can cause hypotension and myocardial ischemia
Carbetocin (synthetic oxytocin analog)	100 micrograms IV	More effective than oxytocin
Methergin (methylergometrine)	0.2 mg IV (slowly)	
15-Methyl PGF2-alpha (carboprost)	250 microgram IM/ intramyometrial	Can cause nausea, vomiting diarrhea, chills. C/I in asthma since it can cause bronchospasm
Misoprostol (PGE1)	1000 microgram per rectum OR 800 microgram sublingual	Can cause fever, tachycardia
Dinoprostone (PGE2)	20 mg per rectum	

Mechanical Methods

- Uterine massage and bimanual compression.
- Uterine tamponade
 - Tight intrauterine packing with sterile gauze for 24 hours (NOT recommended by WHO).
 - Balloon tamponade:
 - **Bakri** balloon (**max 500 ml** capacity)
 - Belfort Dildy Obstetric tamponade System (trade name-**Ebb**, with **upper uterine balloon capacity of 750 ml** and **lower vaginal balloon capacity of 300 ml**).
 - Sengstaken Blakemore tube; Foley catheter; Condom catheter; Rusch urologic balloon.

Surgical Methods

- **B-lynnh compression sutures** or multiple square sutures.
- **Ligation** of: (1) uterine arteries, (2) ovarian and uterine artery anastomosis and (3) anterior division of internal iliac artery
- Angiographic selective arterial embolization.
- Hysterectomy (as a final resort)

EXTRA EDGE

- When uterine atony is due to tocolytic drugs, **calcium gluconate** (1 gram IV slowly) should be given to neutralize the calcium blocking effect of these drugs.
- **Sheehan's** syndrome (postpartum hypopituitarism/pituitary apoplexy) maybe due to severe PPH.

PERINEAL TEAR

Grade	Description
First degree	Injury to perineal skin only, the perineal body remains intact
Second degree	Injury to perineum involving perineal body (muscles) excluding the anal sphincter (Mediolateral episiotomy corresponds to 2nd degree perineal tear)
Third degree (complete)	Involves major lacerations of the posterior vaginal wall and tear of the perineal body including the anal sphincter
Fourth degree	III degree tear + involvement of anal epithelium

Methods to prevent perineal tear

- Ritgen maneuver (promoting flexion of fetal head with left hand and supporting perineum with right hand).
- Episiotomy (does not prevent perineal tear).
- Elective Cesarean section.

Management of Perineal Tear

- First and second degree perineal tear
 - Repaired in **labor room under analgesia** (epidural).
- Third and Fourth degree perineal tear
 - Repair is done in **OT under GA**

PLACENTA ACCRETA

- Aka **Morbidly adherent placenta** - since placenta is directly anchored to the **myometrium**.
- Pathologically
 - **Decidua basalis** and **Nitabuch's fibrinoid layer** are **absent**.
 - Penetration of villi into the muscle layer (**increta**) or upto the serosa (**percreta**).
- Risk Factors: **Placenta previa**; **previous Cesarean section**; prior uterine surgery.
- Diagnosis is made **clinically** only during attempted manual removal of placenta when the plane of cleavage between placenta and uterine wall cannot be made out.
- Management
 - In **focal** morbid adherent placenta: Manual removal of placenta
 - In **total** placenta accreta
 - If woman has completed her family: **Hysterectomy**.
 - If woman has not completed her family: **Conservative approach** (cut the umbilical cord as high as possible and leave the placenta as such).

MALPOSITIONS

- Malpositions refers to position of vertex other than flexed occipitoanterior one.
- **MC malposition** is **right occipitoposterior** position.
- MC in **antropoid or android** pelvis.
- There is **delay in engagement** of head - occipito-posterior position is the **MC cause of non-engagement of head** at term in primigravida patients.
- Mechanism of labor
 - In **favorable circumstances** - **normal delivery** occurs (due to incomplete forward rotation).
 - In unfavorable circumstances, **deep transverse arrest (DTA)** can occur - sagittal suture is placed in the transverse bispinous diameter and there is no progress of the descent of the head.
 - **Cesarean section** is the **management of choice** if **DTA** occurs in android pelvis.

BREECH PRESENTATION

- Breech presentation is the MC malpresentation.
- Types of breech presentation
 - Complete breech/flexed breech (normal attitude of full flexion is maintained)

- Incomplete breech (Varying degrees of extension of thighs or legs are present)
 - Breech with extended legs (**Frank breech**): **MC type** of breech
 - Knee presentation (rare)
 - Footling presentation (rare)
 - In 5% breech presentations, fetal head maybe in extreme hyperextension—'**stargazer**' or '**flying fetus**'.
- **Ultrasonography** confirms the diagnosis
- In Breech - Lie is **Longitudinal**; Presentation is **Podalic**; Denominator is **Sacrum**; MC position is **Left sacro-anterior**.
- In breech presentation the risk of **Cord Prolapse** is **Maximum with footling/knee presentation** and **Least with frank breech**.

Etiology of Breech

- **Prematurity**: MC cause
- **Factors preventing spontaneous version**: Twins; oligohydramnios; septate/bicornuate uterus; short cord; intrauterine death of fetus.
- **Favorable adaptation**: Hydrocephalus; placenta previa; contracted pelvis.
- Multiparae with **lax abdominal wall**
- **Fetal abnormalities**: Trisomy 13, 18, 21; anencephaly; myotonic dystrophy

Management of Breech

- If patient presents with breech at > 36 weeks OR in latent phase of labor, external cephalic version maybe tried.
- **External Cephalic Version**
 - Done in **OPD with NO anesthesia** BUT **continuous fetal monitoring** is needed.
 - Aim is to **convert the breech/transverse lie** into cephalic.
 - Pre-requisites: **gestational age > 36 weeks**, liquor should be **adequate**; membranes should be **intact**.
 - If ECV fails or if patient comes in late labor/active labor, there are 3 options.
 1. **Assisted breech delivery** through the vagina: Vaginal delivery can be done in breech, **ONLY** if **Zatuchni Andros score > 4**; Important maneuvers are described below; for full mechanism, please see OBG textbook.
 2. **Breech extraction**: Where **part or full body of the baby is extracted under GA** by the obstetrician **without** any effort by the patient. Not done these days as it causes trauma to fetus and mother. **ONLY** indication is delivery of second twin if transverse lie and internal podalic version is unsuccessful.
 3. **Cesarean section**

Maneuvers in Breech delivery

- **Lovset** maneuver is for the delivery of the arm in breech presentation
- **Pinard's** maneuver is used in frank breech delivery (to convert frank breech into footling breech)
- Maneuvers used for delivery of after-coming head in breech
 - **Burns Marshall** technique
 - **Bracht** maneuver
 - **Mauriceo-Smaellie-Viet** technique: Malar flexion and shoulder traction
 - **Wigand Martin** technique

EXTRA EDGE

- **Piper's forceps** is specially designed forceps for aftercoming head in assisted breech delivery.

OTHER MALPRESENTATIONS

Face Presentation

- Presenting part is face; denominator is mentum.
- MC position is Left Mento-Anterior.
- MC pelvis is platypelloid.
- MC cause is anencephaly.

Brow Presentation

- Rarest presentation seen in partial extension of head.
- Seen with anencephaly, platypelloid pelvis, multiparity and fetal macrosomia.
- There is no mechanism of labor; delivery is by Cesarean section.

Transverse Lie

- Presentation - **shoulder**.
- MC position is **dorso-anterior**.
- There is NO mechanism of labor; delivery is by Cesarean section.
- Cord prolapse is maximum with transverse lie.

OBSTRUCTED LABOR

- Obstructed labor is one where in spite of good uterine contractions, the progressive descent of the presenting part is arrested due to mechanical obstruction.
- Patient is in agony
- Features of **exhaustion and ketoacidosis**
- Per-abdominally:
 - Since the uterus cannot empty, the thinned lower segment elongates. Sometimes a **palpable ring** (**pathological retraction ring** or **Bandl's ring**) forms between the upper and lower segments.

- **Upper part is hard and tender**
- Fetal **parts** are **not well defined**
- Fetal **heart sounds** are **absent**
- Per-vaginally:
 - Vagina - **dry and hot** - and discharge **offensive**
 - Cervix - fully dilated
 - Membranes - absent.
 - Bandl's ring **cannot** be felt vaginally
- Management is always Cesarean section, whether fetus is dead or alive.

EXTRA EDGE

- Never wait and watch in obstructed labor - can lead to **uterine rupture**.
- **Never give oxytocin** in obstructed labor.
- Obstructed labor is **MC cause of vesicovaginal fistula** in developing countries.
- **Schroeder's ring** is seen in incoordinated uterine action.

Shoulder Dystocia

- Risk factors for shoulder dystocia include ('DOPA!')
 - Maternal **Diabetes**
 - **Obesity** - maternal and fetal, i.e. macrosomia
 - **Post term** fetus
 - **Anencephaly**.

Maneuvers for shoulder dystocia

- McRoberts maneuver (hyperflexing the mother's legs)
- Wood's screw maneuver
- Rubin's maneuver
- Jacquiemer's or Barnum's maneuver
- Gaskin's maneuver
- Zavanelli maneuver (not generally practiced)

PRETERM LABOR

- **Preterm labor** is one where the labor starts **before the 37th** completed week of pregnancy (< **259 days**), counting from the first day of the last menstrual period.
- MC cause is **idiopathic** > infection.
- Most important risk factor is **previous h/o preterm labor**.
- Prophylaxis
 - Stop smoking
 - **Progesterone** decreases uterine activity.
- Clinical features:
 - **Uterine contractions** occurring at frequency of at least 1 in every 10 minutes.
 - Dilatation (> 2 cm) and effacement (80%) of the cervix.
 - Length of cervix < **2.5 cm** and **funneling** of the internal os.
 - Cervix is '**U**' shaped.

- **Fibronectin assay:** Presence of fibronectin glycoprotein produced by fetal amnion in the cervico-vaginal discharge **between 24–34 weeks** is a predictor of preterm labor. If the test is negative - it reassures that the delivery will not occur within the next 7 days.

Management

- **Glucocorticoids:** to the mother to promote fetal lung maturity [See pediatrics chapter for more on this (Pg 667)].
- **Magnesium sulfate** to the mother (neuroprotection) to reduce neonatal cerebral palsy when pregnancy is < 34 weeks.
- Antibiotics: to prevent **group B streptococcal** infection
- **Tocolytic agents** to the mother to reduce uterine contraction; should be preferably avoided as there is no clear benefit.

Tocolytic drugs

- These are drugs that **decrease uterine motility**. They have been used to delay or **postpone labor, or arrest threatened abortion** and in **dysmenorrhea**.
 - Calcium channel blockers: especially **nifedipine**.
 - Adrenergic agonists (**beta 2 agonists** like ritodrine, isoxsuprine, terbutaline) - increased maternal mortality, **pulmonary edema**. DO NOT use in mother with DM, heart disease, on beta blockers or steroids.
 - **Atosiban** (Oxytocin antagonist)
- NO LONGER recommended: Prostaglandin synthesis inhibitors (indomethacin - causes **closure of PDA**); Ethyl alcohol; Magnesium sulfate (causes **pulmonary edema**); progesterone, general anesthetics, nitrates.

DEVIATIONS FROM NORMAL LABOR

- **Prolonged labor:** When the combined duration of the first and second stages of labor is more than the arbitrary time limit of **18 hours**.
- **Premature Rupture of Membranes (PROM):** Spontaneous rupture of membranes anytime beyond the 28th week of pregnancy but before the onset of labor is called PROM. Preterm PROM (PPROM) is defined as PROM **before 37 completed weeks**.

Summary of Abortions

Type	Symptoms	Uterus size	Cervix (Ext. os)	Ultrasound	Management
Threatened	Vaginal bleeding, Pelvic pain	Corresponds to Gestational Age (GA)	Closed	Fetus alive; retro-placental hemorrhage	Reassure; Avoid intercourse
Inevitable	Vaginal bleeding, Pelvic pain	Corresponds to GA	Open with palpable conceptus	Fetus often dead; retro-placental hemorrhage	Insert vaginal misoprostol to complete the process

Contd.

- **Post-term pregnancy (Post-maturity):** Pregnancy continuing **beyond 2 weeks** of the expected date of delivery (> **42 weeks** or >**294 days**).
- **Precipitate labor:** When the combined duration of the first and second stage is < **3 hours** it is called precipitate labour.
- **Arrest of labor:** It is identified when there is NO further dilatation of the cervix for a minimum period of **2 hours** in the active phase.

EXTRA EDGE

- The presence of a pool of amniotic fluid in the posterior fornix on speculum examination is confirmatory of **PROM**.

ABORTION

- **Definition:** Abortion is the expulsion or extraction from its mother of an embryo or fetus weighing **500 g or less** when it is not capable of independent survival (WHO). This 500g of fetal development is attained approximately at **22 weeks (154 days)** of gestation.
- Miscarriage = Spontaneous abortion.
- About **75%** abortions occur **before 16th week** and of these 80% (i.e. overall **55%**) **occur before the 12th week** of pregnancy.
- **Recurrent abortion:** defined as **3 or more** consecutive spontaneous abortions **before 20 weeks**.

MC in Etiology of abortions

- MC cause of **spontaneous** abortion: **Chromosomal** abnormality/**genetic** factors/defective germplasm
- MC cause of **I trimester** abortion: **Chromosomal** abnormality/**genetic** factors/defective germplasm
- MC **chromosomal abnormality** causing abortion: **Aneuploidy** (alteration in number of chromosomes); MC is trisomy (**trisomy 16**)
- MC **specific** chromosomal anomaly a/w abortions: **Mosomy X**
- MC cause of **II trimester** abortion: **Cervical incompetence** (cervico-uterine or anatomical factors)
- MC cause of **recurrent I trimester** abortion: **Idiopathic** (unknown)
- MC chromosomal abnormality in **recurrent I trimester** abortion: **balanced translocation**

Contd...

Type	Symptoms	Uterus size	Cervix (Ext. os)	Ultrasound	Management
Incomplete	Vaginal bleeding	Smaller than GA	Open	Products of conception partly retained	Suction Evacuation
Complete	Vaginal bleeding (trace or absent)	Smaller than GA	Closed	Empty uterus	—
Missed	Vaginal bleeding - traces, Brown color	Smaller than GA	Closed	Blighted ovum or fetus with no fetal heart beat	Uterus < 12 weeks: wait for spontaneous expulsion Uterus > 12 weeks: Misoprostol or D&E
Septic	Vaginal discharge; purulent, foul smelling with features of sepsis	Variable	Open	Products of conception retained; maybe presence of foreign body; free fluid in the peritoneal cavity/ pouch of Douglas	Antibiotics; Analgesics; Anti gasgangrene serum, Anti tetanus serum; Evacuation of uterus

Cervical Incompetence

- Cervical incompetence is a clinical diagnosis manifested with recurrent painless cervical dilatation and spontaneous miscarriage.
- **Hegar no. 6 and 8** dilator can be passed beyond the internal os.
- USG diagnosis during pregnancy: **short cervix < 2.5 cm** length and **funneling** of internal os > 1 cm.
- It can lead to **preterm labor**.
- **Cervical index** = (Funnel length - 1)/Endocervical length; Normal = 0.32; **0.52** indicates incompetent cervix.
- Treatment is by **cervical cerclage stitches** done at **14 weeks** of pregnancy and removed by **36 weeks** of pregnancy.
- **Shirodkar's** operation and **McDonald's** operation are the two MC cerclage operations with almost equal success rates.

MTP ACT

- Medical Termination of Pregnancy (MTP) act (**1971**) was amended last in **2003**.

Who can perform MTP?

- A registered medical practitioner (RMP) can perform MTP provided (a) one has **assisted in at least 25 MTP** in an authorized center having a certificate (b) one has got **6 months house surgeon training in OBG** (c) one has got **diploma or degree in OBG**.
- MTP can ONLY be done in hospitals established or maintained by the **government** or **places approved** by the government.

Contd...

Contd...

Who can perform MTP?

- Pregnancy can only be terminated on written consent of the woman. **Husband's consent** is **NOT** required.
- Pregnancy in a **minor girl (< 18 years of age)** or **lunatic** cannot be terminated without **written consent of parents or guardian**.
- MTP is **permitted upto 20 weeks** of pregnancy. When pregnancy extends **beyond 12 weeks**, **opinion of 2 medical practitioners** is required.
- MTP has to be performed **confidentially** and reported to the **Director of Health services** of the state in the prescribed form.

Indications for MTP

- **To save the life of the mother** (Therapeutic or medical termination) in the following cases: (1) Cardiac diseases (grade III or IV) with h/o cardiac failure in previous pregnancy or in between pregnancies, (2) Malignant hypertension, (3) Intractable hyperemesis gravidarum, (4) Chronic glomerulonephritis, (5) Cervical or breast malignancy and (6) Epilepsy or psychiatric illness with advise of psychiatrist.
- **Social indications:** 'to prevent grave injury to the physical or mental health of the woman.' **Unplanned pregnancy, unwanted pregnancy** and **pregnancy due to rape** come under this category.
- **Eugenic:** If there is substantial risk of child being born with serious physical and mental abnormalities so as to be handicapped in life. Includes **anencephaly**, exposure to **radiation or teratogenic** drugs or first trimester **Rubella**.

Methods of MTP

First trimester (upto 12 weeks)	Second trimester (13–20 weeks)
Surgical <ul style="list-style-type: none">Menstrual regulationVacuum aspiration (MVA or EVA)Surgical evacuation and/or curettageDilatation and evacuation: Rapid/slow method	<ul style="list-style-type: none">Dilatation and evacuation (13–14 weeks)Intrauterine instillation of hyperosmotic solutions<ul style="list-style-type: none">Intra-amniotic hypertonic urea (40%), saline (20%)Extra-amniotic ethacridine lactate, prostaglandins (PGE2, PGF2α)Extra-amniotic saline infusion (isotonic) with a transcervical catheter balloon.
Medical <ul style="list-style-type: none">Mifepristone (Ru486)Mifepristone and misoprostol (PGE1)Methotrexate and misoprostolTamoxifen and misoprostol	<ul style="list-style-type: none">Prostaglandins PGE1 (misoprostol), 15 methyl PGF2α (carboprost), PGE2 (dinoprostone), and their analogues (used intravaginally, IM or intramniotically)Oxytocin infusion high dose used along with either of the above 2 methodsHysterotomy (abdominal)—less commonly done

MULTIPLE PREGNANCY/TWINS

- Simultaneous development of *two fetuses (twins)* in the uterus is the **MC** form of multiple pregnancies.
- Zygosity** refers to the type of conception and genetic makeup.
- Chorionicity** refers to the placental membrane status.

Zygosity

	Monozygotic twins (20%)	Dizygotic twins (MC, 80%)
Origin	Arise from splitting of single fertilized ovum and hence are always of the same sex and look alike	Arise from fertilization of two ova by two sperms; sex of the babies maybe same or different
Placenta	1	2 (mostly fused)
Communicating vessels	Present	Absent
Intervening membranes	2 (amnions)	4 (2 amnions, 2 chorions)

Contd...

Contd...

	Monozygotic twins (20%)	Dizygotic twins (MC, 80%)
Genetic features (blood group, DNA fingerprint)	Same	Differ
Skin grafting (reciprocal)	Acceptance	Rejection
Follow-up	Usually identical	Not identical

Chorionicity

- In **dizygotic** twins - each twin has its own placenta, chroion and amnion, i.e. dizygotic twins are **always diamniotic dichorionic!** (2 chorions and 2 amnions).
- In **monozygotic** twins - the *time at which the fertilized ovum divides* - decides the chorionicity (as below).
 - < 3 days (i.e. *before morula stage*) - Dichorionic, Diamniotic.
 - 4-8 days - **MonoChorionic**, Diamniotic (**MC** type).
 - > 8 days - Monochorionic, Monoamniotic.
 - > 14 days - Conjoined twins
- Chorionicity is **important since** dichorionic twins (either mono or di-zygotic) always develop as two distinct individuals and are NOT at increased risk of complications. BUT **monochorionic twins are at increased risk of complications** due to vascular anastomoses between the two circulations.
- Chorionicity can be detected by **ultrasound between 10–14 weeks** gestation (see following table).



Fig. 24.2: Twin—dichorionic diamniotic



Fig. 24.3: Twins—monochorionic

U/S Features of Chorionicity

	Monochorionic	Dichorionic
Placenta	1	2
Membrane	< 2 mm thick	> 2 mm thick
Layers in membrane	2 (2 amnion)	4 (2 amnion + 2 chorion)
Twin peak/Lambda sign	Absent	Present

EXTRA EDGE

- Hellin's Rule:** According to this rule, the mathematical frequency of multiple births is - twins 1 in 80, triplets 1 in (80)², quadruplets 1 in (80)³ so on.
- Incidence** of twins: HIGHEST in Nigeria (1 in 20); LOWEST in Japan; In India (1 in 80).

Etiology

- Frequency of monozygotic twins remains constant throughout the globe.
- Prevalence of dizygotic twins increased with
 - Increased maternal age
 - Increased parity
 - Maternal family h/o twinning
 - Ovulation inducing drugs: clomiphene

Conjoined Twins

- Aka **Siamese** twins (Thailand).
- Thoracopagus** (fusion at chest) is MC type
- Omphalopagus (Xiphopagus): fused at anterior abdominal wall
- Pyopagus: fused at buttock

- Ischiopagus: fused at ischium
- Craniopagus:** fused at head (least common)

Complications Only in Monochorionic Twins

- Twin-Twin Transfusion Syndrome (TTTS)**
 - Exclusive to monochorionic twins.
 - Donor twin is growth restricted, hypovolemic and is anemic.
 - Quintero's** staging system classifies TTTS; **Ascites or frank hydrops** is **stage IV**
- Twin Reversed Arterial Perfusion (TRAP). (**Acardiac** perfused twin)
- High perinatal mortality (due to monoamnicity)
- Discordant** twins (unequal sizes of twins with a difference of 25% is called discordant growth).

Other Complications of Multiple Pregnancy are

- Maternal:
 - Nausea/vomiting; Anemia; PIH and Preeclampsia; Poly/Oligohydramnios; Antepartum hemorrhage; Postpartum hemorrhage; Malpresentation; Preterm labor; Prolonged labor; More operative interference; Mechanical distress (dyspnea, palpitation).
- Fetal:
 - Abortion; Vanishing twin (*fetus papyraceous*); Appearing twin; Preterm birth; fetal anomalies; IUFD of one fetus; Cord prolapse; Locked twins.

THIRD TRIMESTER BLEEDING

Abruptio Placentae

- Premature detachment** of placenta from implantation site.
- Clinically: **Painful vaginal bleeding** (usually during 3rd trimester); fetal distress.
- Diagnosis: **primarily clinical**; U/S has low sensitivity.
- Treatment: Mild abruptio—bed rest and fetal monitoring; Sever abruptio or fetal distress: Cesarean section
- Tendency of **recurrence** in **next pregnancy** is **10-fold**
- Complications:** DIC, hemorrhagic shock, fetal death
- Prevalence of abruptio placentae is **more with:**
 - HTN or Pre-eclampsia, multigravida 5 and above, Advancing age, Poor patient, Malnutrition, Folic acid deficiency, Abdominal Trauma, Sudden uterine decompression, Short cord, Supine hypotension syndrome, Torsion of uterus, Sick placenta, Cocaine abuse, Smoking, Thrombophilias.

Classifications of Abruptio Placentae

Sher and Statland's Clinical classification	PAGE's classification
<ul style="list-style-type: none">Grade 1 (Mild) - Not recognized clinically before delivery; 'Retrospective' diagnosis made by seeing the presence of retroplacental clot.Grade 2 (Moderate) - Clinical signs of abruptio are present + fetus is ALIVE + fetal heart rate abnormalities presentGrade 3 (Severe) - Clinical signs of abruptio are present + fetus is DEAD + DIC present (3A) or DIC absent (3B); Heavy maternal bleeding + maternal SHOCK present	<ul style="list-style-type: none">Grade 0 - Retrospective diagnosis after deliveryGrade 1 - External bleeding, uterine tenderness and NO fetal distressGrade 2 - Fetal distress or IUFDGrade 3 - maternal shock with/without DIC

Placenta Previa

- Abnormal placental implantation near the cervical os.
- Minor Placenta Previa: Type I, IIA
- Major Placenta Previa: IIB, III, IV
- Dangerous Type** of placenta Previa is type IIB (type II posterior)
- Stallworthy sign:** Slowing/irregular fetal heart rate on pressing the head down into the pelvis and prompt recovery on release of pressure is termed Stallworthy's sign in case of low lying posterior placenta praevia
- Risk factors:** Prior C-section, grand multiparas, multiple gestations, prior placenta previa.
- Clinically: **Painless vaginal bleeding** in 2nd or 3rd trimester.
- Diagnosis: U/S for placental position (**transvaginal U/S** is the gold standard).
- Treatment: Bedrest; if fetal lungs immature use tocolytics to delay labor; if mature C-section delivery.
- Complications: ↑ risk of **placenta accreta**, persistent hemorrhage requiring hysterectomy.
- McAfee Johnson regime** is for the expectant treatment of placenta previa.

PUERPERIUM

- Puerperium** is the period following childbirth during which the body tissues, especially the pelvic organs revert back to the prepregnant state both anatomically and physiologically.
- Puerperium begins as soon as the placenta is expelled and lasts for **approximately 6 weeks** when the uterus becomes regressed almost to the nonpregnant state:

- Involution of uterus** complete by = **6 weeks**.
- Lochia** is the vaginal discharge for the **first fortnight** during puerperium.
- Weight loss** - In addition to the weight loss as a consequence of the expulsion of the uterine contents, a further loss of about **2 kg** occurs during puerperium chiefly caused by **diuresis**.
- Ovulation** returns:
 - In **nonlactating** mothers: by **4 weeks** after delivery
 - In **lactating** mothers: by **10 weeks** after delivery.

EXTRA EDGE

- The correct order of Lochia is:
 - lochia **Rubra** (red) - 1-4 days
 - lochia **Serosa** (yellow brown) - 5-9 days
 - lochia **Alba** (white) - 10-15 days
- Mnemonic: '**RuSsIA**'

MEDICAL DISORDERS IN PREGNANCY

Hyperemesis Gravidarum

- Refractory vomiting** leading to weight loss typically **persisting beyond 14-16 weeks of gestation**.
- Risk factors include: **nulliparity, multiple pregnancies and trophoblastic disease**.
- Hyponatremia with hypochloremic, hypokalemic metabolic acidosis.
- If weight loss/dehydration is present, hospitalize and give antiemetics, IV hydration and electrolyte replacement.
- Other **risk factors:** family history; young age; low body mass; h/o motion sickness and migraine; more common in unplanned pregnancy.
- Transient hyperthyroidism** may occur.

Pregnancy Induced Hypertension-Preeclampsia and Eclampsia

- Preeclampsia** = triad of **hypertension, proteinuria and edema**.
- Mild preeclampsia = BP > 140/90 mmHg on ≥ 2 occasions and proteinuria > 300 mg/24 hrs after 20 weeks of gestation.
- Severe preeclampsia can be a/w:
 - SBP > 160/110 mmHg on ≥ 2 occasions and proteinuria > 5g/24 hrs after 20 weeks of gestation.
 - HELLP** syn (Hemolysis Elevated Liver enzymes and Low Platelets)
 - CNS** (headache, blurred vision, seizures, coma)
 - Renal dysfunction** (oliguria or creatinine > 1.5 mg/dL)

- Pulmonary edema**
- Hepatocellular injury** (ALT > 2-fold the upper limits of normal), hematologic dysfunction (platelet count < 100,000/L or DIC)
- Placental dysfunction (**oligohydramnios** or **severe IUGR**).
- Eclampsia** = **Preeclampsia + seizures**.
- Antepartum** eclampsia is **MC** - fits occurring before the onset of labor
- Risk factors for preeclampsia Include:
 - Nulliparity**
 - Diabetes mellitus**
 - A history of renal disease or chronic hypertension
 - A prior history of preeclampsia
 - Extremes of maternal age (>35 years or <15 years)
 - Obesity**
 - Antiphospholipid antibody syndrome
 - Multiple gestation.
- Treatment:
 - Deliver of fetus** as soon as viable—**definitive treatment** (vaginal delivery is preferred).
 - Otherwise bed rest, salt restriction and control of BP with hydralazine +/- labetalol/nifedipine (AVOID ACE inhibitors or ARBs).
 - Magnesium sulfate** is **treatment of choice** to control **seizures** (prevents seizures by interacting with **NMDA receptors** in the CNS).
 - Regimens of Magnesium sulphate for treatment of eclampsia are (1) Intramuscular (**Prithard**) regimen and (2) Intravenous (**Zuspan** or **Sibal**) regimen.
 - Therapeutic levels** of serum magnesium should be **4-7 mEq/L**. Earliest sign of magnesium toxicity - **loss of deep tendon reflexes**. **Antidote** is Inj. **Calcium gluconate**.
 - Magnesium is **contraindicated** in renal impairment; myasthenia gravis (since it decrease ACh release).

Gestational Diabetes Mellitus (GDM)

- Diabetes mellitus **diagnosed during pregnancy**.
- Risk factors:** Obesity, family history, prior history of DM in pregnancy.
- Treatment:** Diet and exercise. If blood sugars still high after 1 week of therapy, start insulin; can consider **glyburide** and **metformin**.
- Complications of GDM:
 - Fetal:** Congenital malformations, stillbirth, IUGR, hypoglycemia, birth trauma (due to larger fetus), shoulder dystocia, polycythemia, hyperbilirubine-

mia. Children are at ↑ risk of being obese in childhood/adulthood

- Maternal:** Perineal trauma from macrosomic infant, ↑ lifetime risk of developing DM (50%)
- Note:** Clinical features of '**Infant of diabetic mother**' are given in Pediatrics chapter (Pg 668).

Diagnosis of GDM

'One-step' method	'Two-step' method										
<ul style="list-style-type: none">Perform a 75 g oral GTT between 24-28 weeks gestation. It is done after an overnight fast of at least 8 hours.Diagnosis of GDM is made when any of the below levels are high.<ul style="list-style-type: none">Fasting - 92 mg/dL1 hour - 180 mg/dL2 hour - 153 mg/dL	<ul style="list-style-type: none">Perform a 50 g oral GTT (Step 1) between 24-28 weeks gestation.If plasma glucose at 1-hour is > 140 mg/dL, proceed to 100 g oral GTT (step 2).Diagnosis of GDM is made when at least two of the below four levels are high.<table><tr><th>Time</th><th>Plasma glucose level</th></tr><tr><td>Fasting</td><td>95 mg/dL</td></tr><tr><td>1 hour</td><td>180 mg/dL</td></tr><tr><td>2 hours</td><td>155 mg/dL</td></tr><tr><td>3 hours</td><td>140 mg/dL</td></tr></table>	Time	Plasma glucose level	Fasting	95 mg/dL	1 hour	180 mg/dL	2 hours	155 mg/dL	3 hours	140 mg/dL
Time	Plasma glucose level										
Fasting	95 mg/dL										
1 hour	180 mg/dL										
2 hours	155 mg/dL										
3 hours	140 mg/dL										

Maternal Hyperthyroidism

- MC cause is **Grave's disease**.
- Drug of choice** is **propylthiouracil**; **radioiodine** is **strictly contraindicated**.
- Note:** **Methimazole** crosses placenta to a greater degree; it is a/w fetal aplasia cutis and esophageal and choanal atresia; propylthiouracil is a/w fetal hepatotoxicity). HENCE use propylthiouracil in first trimester and switch over to methimazole for later part of pregnancy (H-18th and CMDT 2013).

EXTRA EDGE

- In cases of **hypothyroidism**, pre-pregnancy levothyroxine levels have to be **increased by '30%'** as soon as pregnancy is detected.

Heart Disease in Pregnancy

- Valvular Heart Disease:** This is the **MC cardiac problem** complicating pregnancy.
- Mitral stenosis:** valvular disease **most likely to cause death** during pregnancy.
- Mitral regurgitation and aortic regurgitation and stenosis:** generally **well tolerated** during pregnancy.

Conditions a/w a particularly high risk for maternal death and considered contraindications to pregnancy

- **Eisenmenger syndrome**
- **Primary pulmonary hypertension**
- **Marfan syndrome with aortic root dilatation**, and
- **Severe aortic or mitral stenosis.**

Intrahepatic Cholestasis of Pregnancy

- **Pruritus** (jaundice in only 10–25%); **Markedly increased fasting serum bile acids**
- **Spontaneous resolution** of signs and symptoms post delivery or MTP.

Antiphospholipid Syndrome

- Presence of specific autoantibodies a/w arterial and venous thrombosis and adverse pregnancy outcomes (three or more consecutive spontaneous abortions prior to 10 weeks gestation, one fetal loss after 10 weeks gestation, or a preterm delivery at less than 34 weeks due to preeclampsia)
- Lab: **Antiphospholipid antibodies**: the **lupus anticoagulant**, **anticardiolipin antibodies**, or **anti-beta 2-glycoprotein I antibodies**.
- Treatment: It is subcutaneous **LMWH and low-dose aspirin**.

Acute Fatty Liver of Pregnancy

- Occurs in the **third trimester** of pregnancy (**after the 35th week**); more common in **primigravidas** and those with **twins**.
- Maybe the result of **poor placental mitochondrial function** OR **fetal deficiency of long-chain acyl coenzyme A dehydrogenase (LCHAD)**.
- **Fatty engorgement of hepatocytes** and involves **acute hepatic failure**.
- **Immediate delivery** is treatment of choice (**vaginal delivery preferred**).

ECTOPIC PREGNANCY

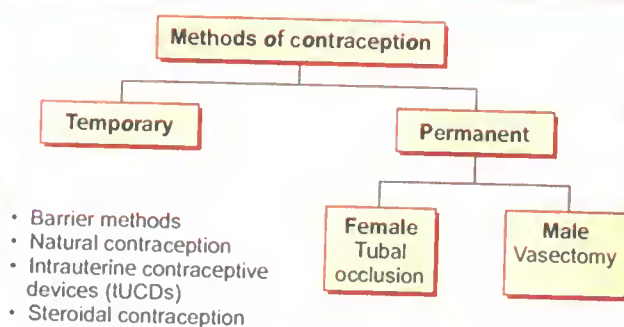
- Implantation of **fertilized ovum outside the uterus**.
- **Ampulla** of the fallopian tube is the MC site; **ovary, cervix and abdominal cavity** may also be involved.
- **Risk factors**:
 - Pelvic inflammatory disease (PID)
 - h/o STD
 - Prior ectopic pregnancy

- Prior gynecologic surgery
- Multiple sex partners
- Progestogen only pill
- **Clinically: abdominal pain** (becomes severe if ectopic ruptures); vaginal bleeding, pelvic mass.
- **Diagnosis**:
 - ↑**β-hCG** with U/S unable to locate intrauterine pregnancy. β-hCG for intrauterine pregnancy should double every 48 hours, so a β-hCG level that is low for the time of gestation should raise the suspicion of ectopic pregnancy.
 - U/S should be able to visualize a pregnancy once the β-hCG level reaches 6,500 IU/mL for transabdominal U/S and 2,000 IU/mL for transvaginal U/S.
- Treatment:
 - **Unruptured ectopic < 6 weeks (< 3.5 cm diameter)** - **IM methotrexate** to induce abortion;
 - **Ruptured ectopic** - **laparoscopic** surgical excision.

"Most Common's" in Ectopic Pregnancy

- Most common site of ectopic pregnancy = **Fallopian tube**
- Most common site in fallopian tube = **Ampulla (rarest is interstitial)**
- Most common site of rupture of ectopic = **Isthmus of fallopian tube**
- Most commonly ectopic pregnancy a/w = **Progestasert or progestin only pills**
- Most common mode of termination of ectopic = **Tubal abortion**

CONTRACEPTION AND BIRTH CONTROL



- **Contraception** includes all measures, temporary or permanent designed to prevent pregnancy due to the coital act.

- **Temporary** methods are commonly used to space or postpone births.
- **Permanent surgical contraception** also called voluntary sterilization is a surgical methods whereby the reproductive function of an individual male or female is purposefully and permanently destroyed.
- **Fertility awareness based methods** are:
 - Natural contraception (rhythm, coitus interruptus and lactational amenorrhea)
 - Barrier methods (condoms; diaphragms and spermicides).
- **Rhythm method** is the **ONLY** method **approved** by the **Roman Catholic** church.

BARRIER METHODS

- **Mechanical**:
 - Male: Condom
 - Females: Condom (femidom); Diaphragm; Cervical cap
- **Chemical (Vaginal contraceptives)**
 - Creams: **Delfen** (nonoxynol-9, 12.5%)
 - Jelly - **Koromex**; **Volpar** paste
 - Foam tablets: Aerosol foams; Chloramine T or Contab; Vaginal contraceptive sponge (**Today**)

Important Points about Barrier Methods

- **Condoms** are made of **polyurethane** or **latex rubber**. It is the **most widely practiced method** by the male.
- Additional advantage of condoms is protection against STDs.
- **Nirodh** is a popular latex condom marked by the government in India.
- **Female condom** is **17cm long** and made of polyurethane which lines the vagina and consists of two flexible polyurethane rings at each end. **Inner ring** is inserted at apex of vagina and outer ring remains outside; it protects against STDs; it is expensive BUT **multiple uses** can be made with washing and drying.
- **Diaphragm** is an intravaginal device made of latex with flexible metal or spring ring at the margin; Its diameter varies from 5–10 cm and required medical/paramedical personnel to accurately measure the diameter required. The distance between the tip of the middle finger placed in the posterior fornix and the point over the finger below

the symphysis pubis gives the approximate diameter of the diaphragm. The diaphragm is introduced **upto 3 hours before intercourse** and is to be kept **for at least 6 hours after the last coital act**.

- **Spermicides** are available as vaginal foams, gels, creams and tablets. usually they contain surfactants like nonoxynol-9; octoxynol or benzalkonium chloride.
- **Vaginal contraceptive sponge (Today)** is made of polyurethane which is impregnated with 1g of nonoxynol-9 as spermicide. Nonoxynol-9 immobilizes and kills sperms. It releases spermicide during coitus, absorbs ejaculate, and blocks the entrance to the cervical canal. Sponge should not be removed for 6 hours after intercourse.

NATURAL CONTRACEPTION

1. Rhythm Methods

Temperature method

Following ovulation, a woman's Basal Body Temperature (BBT) will rise by 0.2–0.4°C because after ovulation progesterone is secreted by the corpus luteum, which causes a woman's BBT to rise, where it will stay until the next period.

Cervical mucus method (Billing's method)

At the time of ovulation, under estrogen influence the mucus becomes excessive, clear and stretchy and this is called fertile mucus (peak mucus). Four days following peak mucus day, the mucus becomes thick, sticky and opaque because estrogen level has dropped.

Calendar method

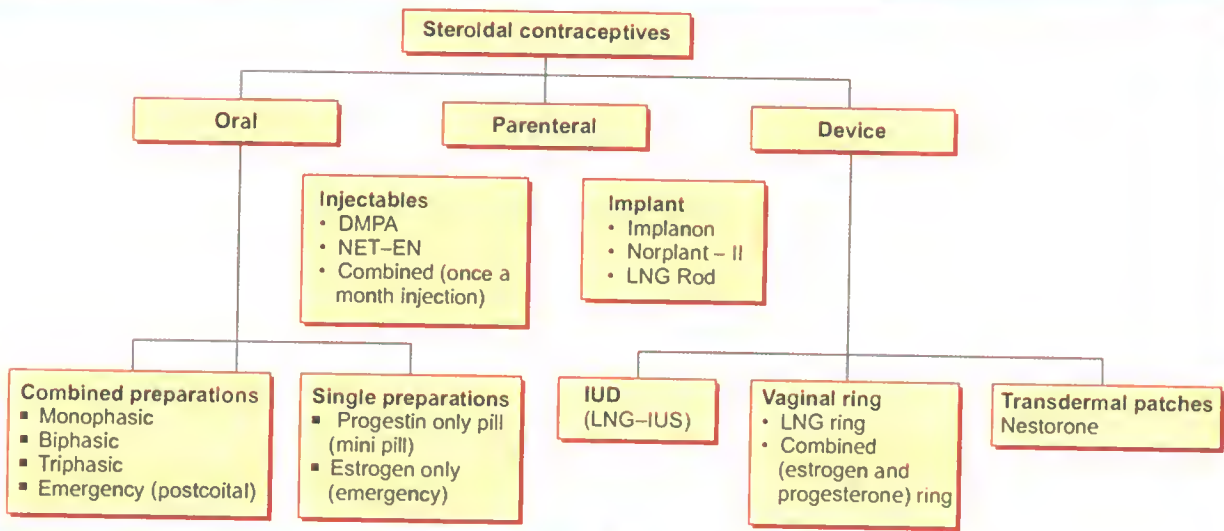
The first unsafe day is obtained by subtracting 20 days from the shortest cycle and the last unsafe day by subtracting 10 days from the longest cycle.

Symptothermal method

Combination of above three methods; also called double check method.

2. **Coitus interruptus**: It necessitates withdrawal of the penis shortly before ejaculation.
3. **Lactational amenorrhea**: Breastfeeding offers a natural protection from pregnancy; risk of pregnancy to a woman who is fully breastfeeding and amenorrheic is < 2% in the first 6 months. When fully breastfeeding a contraceptive method should be used in the 3rd postpartum month and with partial/no breastfeeding she should use it in the 3rd postpartum week.

STEROIDAL CONTRACEPTIVES



INTRAUTERINE CONTRACEPTIVE DEVICE (IUD)

- I generation IUDs = Non-medicated IUDs.
- II generation IUDs = Copper IUDs.
- III generation IUDs = Hormone-releasing IUDs.

Mechanism of Action

- Nonmedicated devices cause biochemical and histologic changes in the endometrium; there may be increased tubal motility; and impaired sperm ascent.
- Copper devices prevent blastocyst implantation through enzymatic interference.
- LNG-IUS (Mirena) - induces strong uniform suppression of the endometrium; cervical mucus becomes scanty.

Timing of Insertion

- IUD can be inserted anytime but is more likely to be expelled during a period or shortly after childbirth (immediate postpartum insertion). Hence it is preferable to insert **2-3 days after the menstrual period** is over or **6-8 weeks after delivery** (post-puerperal insertion). During lactational amenorrhea it can be inserted anytime.

Contraindications to IUDs

- **Absolute:** Suspected pregnancy; pelvic inflammatory disease (PID); vaginal bleeding of undiagnosed etiology; cancer of the cervix, uterus or adnexa and other pelvic tumors; previous ectopic pregnancy
- **Relative:** Anemia, menorrhagia, h/o PID, distortions of the uterine cavity due to congenital malformations or fibroids; caesarian section scar; diabetes, heart disease, nulliparity (newly married woman).

Side Effects

- Increased vaginal bleeding (MC complaint); pain; pelvic inflammation (Actinomyces); uterine perforation; ectopic pregnancy; expulsion; infertility following removal.
- **Open IUCD** - has no circumscribed aperture of more than 5 mm so that a loop of intestine or momentum cannot enter and become strangulated (if accidentally the device perforates the uterus into the peritoneal cavity).
- **Closed devices** like Grafenberg ring and Birnberg bow can cause strangulation and are now obsolete.
- **Copper T 200** - contains 120 mg of copper and carries 200 sq mm surface area of copper wire; removed after 3 years.
- **Copper T 200 B** - contains 124 mg of copper and carries 215 sq mm surface area of copper wire; removed after 4 years. Barium sulfate is incorporated to make it further radio-opaque.
- **Copper T 380A** (Cu T 380 A) - contains 380 sq mm surface area of copper; replaced every 10 years.
- **Multiload Cu 250** (ML-Cu-250) - replaced every 3 years.
- **Multiload Cu 375**: replacement every 5 years.
- Levonorgestrel Intrauterine system (**LNG-IUS; Mirena**): T shaped device with polydimethylsiloxane around the stem which acts as a steroid reservoir. total amount of LNG is 52 mg; replaced every 5 years.
- **Progestasert**: Progesterone (38 mg) containing IUCD; no longer manufactured.
- **Lippes loop**: non medicated IUCD; no longer used in India.

Failure Rates of Contraceptive Methods

- The failure rate of any contraceptive is calculated in terms of pregnancy rate per hundred woman (HMY) years of use. It is expressed as the **Pearl index**.

$$\text{Pregnancy failure rate/HWY} = \frac{\text{No. of accidental pregnancies} \times 1200}{\text{No. of patients observed} \times \text{months of use}}$$

(Pearl index)

- In the above formula 1200 = number of months in 100 years.
- When the pearl index is below 10 the effectiveness of the particular method is considered to be high; if it is more than 20 it is low.
- Failure rates of different methods are given in the table below.

Method	Pregnancy rate per 100 women years
No method	85
Natural Rhythm (calendar, temperature, mucus)	25
Coitus interruptus (withdrawal)	25
Lactational amenorrhea	2
Condom (male)	15
Condom (female)	21
Diaphragm	16
IUCD (CuT 380A)	0.8
IUCD (LNg 20)	0.1
Combined OCP	0.1
Progestin only pill	1
Patch	0.38
DMPA and NET injectables	0.3
Norplant	0.05
Implanon	0.01
Vasectomy	0.15
Tubectomy	0.15

FEMALE STERILIZATION

- Timing of surgery:
 - During puerperium: can be done within 24-48 hours after delivery
 - Interval tubectomy: 3 months after delivery or abortion; ideal time is following menstrual period in the proliferative phase.
- Methods (see also table below):
 - Abdominal tubectomy
 - Conventional (Pomeroy; Uchida; Madlener; Irving; Kroener)

- Minilaparotomy (Uchida)
- Vaginal tubectomy
- Laparoscopic tubectomy
- Hysteroscopic methods.

Methods	Comments
Conventional laparotomy	
Pomeroy's tubectomy	Segment of loop is excised ; Lowest failure rate of 0.4%
Madlener's technique	Loop is NOT excised; abandoned due to high failure rate of 7%
Irving's method	Medial cut end is buried in the myometrium posteriorly and distal cut end is buried in the mesosalpinx; performed at time of C-section
Kroener method	Not a common procedure; a type of fimbriectomy
Uchida method	No failure observed in this method so far
Minilaparotomy (Mini-lap)	
Popularized by Uchida Main method in National Family Planning Program	
Laparoscopic sterilization	
Tubes are occluded by Silastic ring (Falope); Filshie clip or Hulka Clemens spring clip Useful for quick turnover in mass camps	
Hysteroscopic (transcervical) method	
Essure	Microcoil made of nickel titanium steel alloy within which lie polyethylene terephthalate fibers; it is inserted into hysteroscopically each Fallopian tube; success rate is 99.74%; for first 3 months a temporary contraceptive method should be used
Adiana	A combined procedure ; controlled thermal damage to the proximal tubal epithelium is done by radiofrequency energy hysteroscopically; a soft silicone pellet is inserted at the site to stimulate tissue growth; failure rate is 1.1%
Quinacrine pellet	252 mg is inserted into the uterine cavity during the proliferative phase; acts as sclerosing agent ; carcinogenic

MALE STERILIZATION - VASECTOMY

- A segment of the vas deferens of both sides are **resected** and the cut ends are ligated.
- Additional contraceptive methods are to be used **for 3 months** till the semen becomes free of sperm.
- It takes about **20 ejaculations** to empty the stored semen.
- No scalpel vasectomy was popularized by **Dr Li Shun Qiang** of China - now performed commonly in India.

ONGOING TRIALS AND SELECTIVELY AVAILABLE CONTRACEPTIVES

- **Centchroman: (SAHELI): Ormeloxifene**, it is a research product of Central Drug Research Institute (CDRI), Lucknow. It is a non-steroidal estrogen antagonist; works primarily by inhibiting implantation of fertilized ovum.
- **Combined Injectable Contraceptives (CICs):** *Mesigyna and Cycloferm*; Injection is given within first 5 days of menstruation; next injection should be on the same day of each month - currently withdrawn from the market.
- **Transdermal patch: Nestrone**, newer progeston when used as a cream on the skin provides effective contraception. Patch of *norelgestromin* may be used.
- **Uniplant:** single rod implant containing 55 mg of norgestrol; provides contraception for 1 year.
- **Biodegradable Implants: Capnor** (single capsule); effective for 1 year.
- **Newer IUCD - frameless IUCD GyneFix**, is made of 6 copper beads (330 sq mm of Cu) on a *monofilament polypropylene thread*; the thread is knotted at one end which is embedded into the fundal myometrium to a depth of 1 cm; can be removed with a hook when required; specially suited for nulligravid women.
- **Fibroplant** - similar to Mirena but a smaller version.

EXTRA EDGE

- **Condoms are the best choice** for contraception in **HIV positive patients** because they prevent HIV transmission during intercourse. Women who use other contraceptives (such as the pill) should be informed that these pills prevent pregnancy. BUT they do not prevent HIV infection and that they may infect their sexual partners if they do not use condoms as well. (IUCDs NOT recommended).
- The frameless copper IUD (**GyneFix**) is designed for the **nulliparous** patient.

METHODS OF TERMINATION OF PREGNANCY

First trimester (up to 12 weeks)	Second trimester (13–20 weeks)
Surgical <ul style="list-style-type: none">• Menstrual regulation• Vacuum aspiration (MVA or EVA)• Surgical evacuation and/or curettage	<ul style="list-style-type: none">• Dilatation and evacuation (13–14 weeks)• Intrauterine instillation of hyperosmotic solutions<ul style="list-style-type: none">– Intra-amniotic hypertonic urea (40%), saline (20%)– Extra-amniotic ethacridine lactate, prostaglandins (PGE2, PGF2α)

Contd...

Contd...

First trimester (up to 12 weeks)	Second trimester (13–20 weeks)
<ul style="list-style-type: none">• Dilatation and evacuation: Rapid/slow methodMedical<ul style="list-style-type: none">• Mifepristone (Ru 486)• Mifepristone and misoprostol (PGE1)• Methotrexate and misoprostol• Tamoxifen and misoprostol	<ul style="list-style-type: none">– Extra-amniotic saline infusion (isotonic) with a transcervical catheter balloon.• Prostaglandins PGE1 (misoprostol), 15 methyl PGF2α (carboprost), PGE2 (dinoprostone), and their analogues (used intravaginally, IM or intramniotically)• Oxytocin infusion high dose used along with either of the above 2 methods• Hysterotomy (abdominal) – less commonly done

INTRAUTERINE GROWTH RETARDATION (IUGR)

- Defined as estimated fetal weight **at or below the 10th percentile for gestational age**.
- Suspect IUGR clinically if the **difference between fundal height and gestational age is > 2 cm**.
- Causes of IUGR
 - Fetal: Chromosomal abnormalities (Trisomy 21 – MC, also trisomy 18, 13); Infection (CMV MC, toxoplasmosis); placental and uterine abnormalities, multiple gestations.
 - Maternal causes: Hypertension, Drugs (cigarette smoking MC); SLE; malnutrition, thrombophilia.
- **Symmetric IUGR:** Body and head growth are similarly affected. It indicates that cause of IUGR occurred in early pregnancy (first trimester) and was genetic or due to viral infections.
- **Asymmetric IUGR:** Somatic growth (i.e. Abdominal circumference and lower body) shows significant delay BUT head growth is spared. Occurs due to uteroplacental insufficiency.
- Further IUGR has been discussed under Pediatrics Chapter (Pg 704).

HYDATIDIFORM MOLE

- A benign neoplasm of trophoblastic cells (i.e. placental cells) that carries a risk of malignant transformation.
- **Complete mole:** 46, XX; 2 sperm + empty egg; completely paternal in origin.
- **PARTIAL mole:** 69, XXY; 2 sperm + 1 egg; made up of 3 or more PARTs (triploid or tetraploid); may contain fetal PARTs.
- Risk factors: low socioeconomic status, age > 40 years, Asian heritage, tobacco use.

- Suspect in patients with 1st trimester uterine bleeding and excess nausea and vomiting.



Fig. 24.4: Hydatidiform mole (gross view)

- Also suspect if preeclampsia occurs in first half (< 24 weeks) of pregnancy.
- Other signs **uterine size > gestational age** (MC with complete mole); **hyperthyroidism**; **expulsion of "grape-like" vesicles from the vagina**, no detectable fetal heartbeat.
- β -hCG $\uparrow\uparrow$ for gestational age (usually > 100,000 mIU/dL); U/S shows **"snowstorm" appearance** with no gestational sac.
- Treatment: **D and C**; avoid pregnancy for 1 year; monitor β -hCG levels for a year.
- In 20% of cases **choriocarcinoma** may develop. Treat with chemotherapy and residual uterine disease with hysterectomy.

Complete versus Partial Hydatidiform Mole

Feature	Complete mole	Partial mole
Karyotype	46 XX, 46 XY	Triploid, 69, XXY or 69, XYY
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse, circumferential	Focal, slight
Atypia	Often present	Absent
Serum hCG	Elevated	Less elevated
hCG in tissue	++++	+
Behavior	2% choriocarcinoma	Rare choriocarcinoma
Fetal parts	Rarely seen	More common

CESAREAN SECTION (C/S)

- It is an operative procedure whereby the fetus **after the end of 28th week** is delivered through an incision on the abdominal and uterine walls.

- MC method is **Lower Segment C/S (LSCS)**.
- **Absolute indications** for C/S is where vaginal delivery is not possible (even with a dead fetus); conditions are:
 - Central placenta previa
 - Contracted pelvis or cephalopelvic disproportion
 - Pelvic mass causing obstruction (cervical or broad ligament fibroid)
 - Advanced carcinoma cervix
 - Vaginal obstruction (atresia, stenosis).
- Modified Pfannenstiel **incision (low transverse abdominal)** is most preferred. Advantages are:
 - Ease of operation
 - Less bladder dissection
 - Less blood loss
 - Easy to repair
 - Complete repertorization
 - Less adhesion formation
 - **Less risk of scar rupture (0.2-1.5%)** when trial of labor is given for subsequent delivery.
- The optimum interval between uterine incision and delivery should be **less than 90 seconds**.
- The uterine incision is sutured in **three layers**.
- **Mendelson syndrome:** Aspiration pneumonitis following general anesthesia for C/S.

EXTRA EDGE

- **Classical C/S** (through upper segment uterine incision) is **obsolete**.
- **Higher risk of scar rupture (4-9%)** during subsequent pregnancy deliveries.

Prior uterine incision	Estimated scar rupture
Low Transverse	0.2–1.5%
Low Vertical	1–7%
T shaped	4–9%
Classical	4–9%

IMPORTANT POINTS ABOUT OPERATIVE ORTHOPEDICS

Dilatation and Evacuation

- **One stage:**
 - Dilatation of cervix and evacuation of uterus are done in same sitting
 - MC indication is **incomplete abortion**.
 - Cervical dilatation is done by **graduated metal dilators**.

- **Two stage:**
 - First phase includes slow dilatation of cervix; second phase includes rapid dilatation of cervix and evacuation.
 - MC indication is induction of **first trimester abortion (MTP)**.
- Cervical dilatation is done by *laminaria tents*, *lamicel* (MgSO₄ sponge) or intravaginal insertion of *misoprostol* (PGE₁).
- In both the methods above **0.2 mg methergine is given IV** to minimize blood loss during curettage.

SUCTION EVACUATION

- It is a procedure where the products of conception are sucked out from the uterus with the help of cannula fitted to a suction apparatus.
- MC indication is **first trimester abortion (MTP)**.
- The pressure of suction is **400–600 mmHg**.
- The *vacuum should be broken* before withdrawing the cannula (to prevent injury to internal os).

MENSTRUAL REGULATION

- Aka *induction, aspiration*.
- It is the aspiration of the endometrial cavity **within 14 days of missed period** in a woman with a previous normal menstrual cycle.
- Done as an *outpatient procedure*.
- **Karman's suction cannula** is used.
- The procedure is *contraindicated* in advanced pregnancy and is presence of local pelvic inflammation.

VACUUM ASPIRATION

- The procedure is similar to menstrual regulation and done on OPD basis.
- It maybe Manual Vacuum Aspiration (MVA) or Electronic Vacuum Aspiration (EVA) and is *highly effective* (98–100%).
- **MTP upto 12 weeks** is done by this method.
- A *negative pressure of 660 mmHg* is created and procedure takes 10–15 minutes.

EPISIOTOMY

- A surgically planned incision on the perineum and the *posterior* vaginal wall during the **second stage of labor** is called **episiotomy (perineotomy)**.
- It is the **MC obstetric surgery** performed.
- It is in fact and inflicted *second degree perineal injury*.
- Timing of episiotomy: Bulging thinned perineum during at the height of a contraction just prior to crowning

(when 3–4 cm of head is visible). During forceps delivery it is made *after* application of the blades.

- **Mediolateral** episiotomy is MC done.
- If non-absorbable sutures are used it should be *cut on the 6th day*.

FORCEPS

- Obstetric forceps is a pair of instruments specially designed to assist extraction of the fetal head and thereby accomplishing delivery of the fetus.
- Three varieties of forceps are MC used:
 - Long curved forceps with or without axis-traction device (MC used in India - named after Sir Kedarnath Das - Das forceps).
 - Short curved forceps (Wrigley)
 - Kielland's forceps
- The blade which corresponds to the *left of the maternal pelvis is the left blade* and that to the *right side is the right blade*.
- Forceps operation maybe: Outlet forceps; **Low forceps (MC, 90%)** and Midforceps.
- Traction force required in *primigravida* is 20 kg and in *multigravida* is about 13 kg.
- The *left or lower blade is introduced first* and the *right blade is removed first*.

Pre-requisites (Criteria) for Forceps Delivery are:

Fetal and uteroplacental criteria	Maternal criteria
<ul style="list-style-type: none"> • Fetal head must be engaged • Cervix must be fully dilated • Membranes must be ruptured • Position and station of the fetal head must be known with certainty 	<ul style="list-style-type: none"> • No major cephalopelvic disproportion by clinical pelvimetry • Bladder must be emptied • Adequate analgesia • Others • Experienced operator • Verbal or written consent

EXTRA EDGE

- Mnemonic for **F-O-R-C-E-P-S** = F: Favorable head position and station; O = Open Os (fully dilated); R = Ruptured membranes; C = Contractions present and consent; E = Engaged head, Empty bladder; P = Pelvimetry - no major CPD; S = Stirrups and lithotomy position.

VENTOUSE

- Ventouse is an instrumental device designed to assist delivery by creating a **vacuum** between it and the fetal scalp.
- Introduced by **Malmstrom** in 1956.

- **Contraindications** for ventouse delivery are:
 - Any presentation other than vertex (face, brow or breech).
 - Preterm fetus (< 34 weeks).
 - Suspected fetal coagulation disorder.
 - Suspected fetal macrosomia (> 4 kg).
- The suction cup is placed against the fetal head *nearer the occiput (flexion or 'pivot' point)*.
- The *effective vacuum pressure* is **0.8 kg/cm²**
- The scalp is sucked into the cup and an **artificial caput (chignon)** is produced which disappears within few hours.

Indications for Operative Vaginal Delivery (Foreceps/Ventouse)

Maternal	Fetal	Others
<ul style="list-style-type: none"> • Inadequate expulsive efforts • If mothers is exhausted (maternal distress) • When expulsive efforts (Valsalva) are to be avoided (e.g. cardiac disease, HTN crisis, spinal cord injury, cerebrovascular disease) 	<ul style="list-style-type: none"> • After-coming head of breech • Suspicion of fetal compromise • Nonreassuring fetal heart rate - fetal distress (e.g. LBW baby, postmaturity) 	<ul style="list-style-type: none"> • Prolonged second stage of labor (nullipara > 2 hours; multipara > 1 hour) • To cut short the second stage of labor as in severe pre-eclampsia, cardiac disease, post cesarian pregnancy)

Complications of Forceps and Ventouse

Maternal complications are more common with **forceps**, while **fetal** complications are more common with **Ventouse**.

Fetal complications more common with **Ventouse** are:

- Hemorrhages: Subgaleal; Intracerebral; Retinal; Cephalhematoma
- Neonatal jaundice
- Transient lateral rectus paralysis
- Shoulder dystocia

Fetal Complications more common with **Forceps** are:

- Facial and brachial nerve palsies.

VERSIONS

- **Version** is a manipulative procedure to change the lie of the fetus or to bring the comparatively favorable pole to the lower pole of the fetus.
- **External cephalic version:**
 - Indications are **breech** presentation and **transverse** lie.

- Success rate of ECV is about **60%**.
- **Internal version** — the **ONLY** indication in modern day is **transverse lie in case of second baby of twins**.

DESTRUCTIVE OPERATIONS

- Craniotomy
- Decapitation
- Cleidotomy
- Evisceration

SMOKING AND PREGNANCY

Smoking related maternal complications	Smoking related fetal complications
<ul style="list-style-type: none"> • Spontaneous abortion • Preterm delivery • Ectopic pregnancy • Placenta previa • Abruption placentae • Preterm premature rupture of membranes 	<ul style="list-style-type: none"> • IUGR/Low birth weight • Sudden infant death syndrome (SIDS) • Increased orofacial clefts in the fetus • Developmental lag for first few years of life: adverse effects on language skills and visual and spatial abilities.

FETAL ALCOHOL SYNDROME

Even moderate drinking of alcohol during pregnancy can result in fetal alcohol syndrome. It consists of

- Prenatal-onset **growth deficiency**
- Developmental *delay*
- **Microcephaly, Holoprosencephaly** and **agenesis of corpus callosum**
- Facial dysmorphism (short palpebral fissures, ptosis, strabismus, ear abnormality, long philtrum with a thin upper lip)
- Multiple joint anomalies
- Cardiac defects (**ASD** > **VSD**)
- ADHD and mental subnormality
- Increased breech presentation

MORE HIGH YIELD POINTS

- **Elderly primigravidae:** First pregnancy at or above the age of 35 years.
- **Grand multipara:** Pregnant mother who has got four or more viable births.
- **Bad Obstetric History:** Pregnant mother when her present obstetric outcome is likely to be affected adversely by the nature of previous obstetric disaster
- Suspect IUGR clinically if the difference between fundal height and gestational age is **> 2 cm**.
- **Puerperal mastitis** MC cause is **Staph aureus**.
- Mainstay of treatment for **primary dysmenorrhea** is **NSAIDs**.

- **Condoms** are the best choice for contraception in HIV positive patients because they prevent HIV transmission during intercourse. Women who use other contraceptives (such as the pill) should be informed that these pills prevent pregnancy, BUT they do not prevent HIV infection and that they may infect their sexual partners if they do not use condoms as well. (IUCDs NOT recommended).
- **Nipple confusion** occurs due to alternating between breast and bottle feedings.
- **PNDT** (Prenatal Diagnostic Techniques) ACT was introduced in 1994. In 2003, **PCPNDT** act was passed (PreConception and PNDT) act.
- The frameless copper IUD (GyneFix) is designed for the nulliparous patient.
- The recommended timing of elective Caesarian section (or Caesarian section on maternal request) is 39 weeks of gestation.
- In untreated HIV mothers, there is a 15-30% risk of MTCT.
- In postmenopausal bleeding, **endometrial thickness** > 4 mm by transvaginal sonography is an indication for D&C.
- **Spiegelberg criteria** are for **ovarian ectopic** pregnancy.



Fig. 24.5: Episiotomy scissors



Fig. 24.6: Vacuum extractor (manual)

CHAPTER

25

Gynecology

ANATOMY OF FEMALE PELVIC ORGANS

Female External Genitalia

- **Vulva** = collective name for **external genitalia** (mons pubis, labia majora and labia minora, vestibule) + **perineum**.
- The **labia majora** lie on either side and join posteriorly to form the posterior commissure; they are **homologous with the scrotum** in the male. The round ligaments terminate at its upper border. It contains hair follicles, sebaceous glands and apocrine sweat glands.
- The **labia minora** is a thin fold of skin homologous to the **ventral aspect of the penis**. It does **NOT** contain hair follicles. **Anteriorly** they **enclose the clitoris** and **posteriorly** the labia minora fuse across the midline to form the **fourchette**.
- **Clitoris** is homologous to the **penis**.
- **Vestibule** is a triangular space bounded anteriorly by the clitoris; posteriorly by the fourchette and on either side by the labia minora. It contains 4 openings: **Urethral** opening; **Vaginal** opening; **Bartholin's ducts** on either side and ducts of **paraurethral glands** of Skene.
- The posterior part of the vestibule between fourchette and vaginal opening is called **fossa navicularis**.
- During childbirth the hymen is extremely lacerated, later represented by cleavaged nodules—**caruncular myrtiformis**.

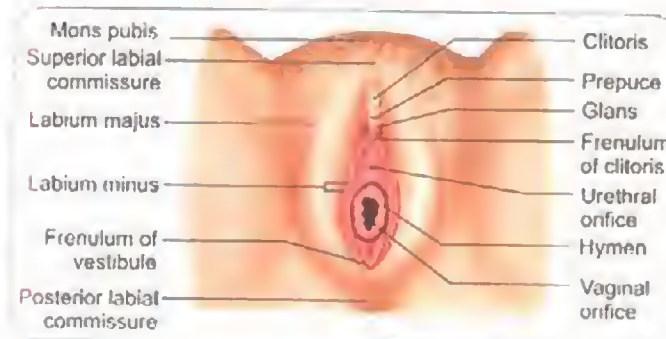


Fig. 25.1: Female external genitalia

- Blood supply of vulva - **Internal pudendal** artery.
- Nerve supply of vulva - **pudendal** nerve.
- Lymphatic drainage of vulva - **Inguinal** nodes.
- Lymphatic drainage of clitoris - lymph nodes of **Cloquet** (**Rosenmuller** lymph nodes).

Development of external genitalia

- Clitoris—from genital tubercle
- Labia minora—from genital folds
- Labia majora—from labioscrotal swellings
- Vestibule—from urogenital sinus

Homologous Glands in Males and Females

Males	Females
Prostate gland	Skene's paraurethral glands
Cowper's gland	Bartholin gland
Glands of Littre (in penile urethra)	Glands of labia majora and minora

Vagina

- **Development of Vagina**
 - **Upper 4/5** above the hymen - The mucus membrane is derived from the endoderm of the canalized **sino-vaginal bulbs**. Musculature is developed from mesoderm of two fused **Mullerian ducts**.
 - **Lower 1/5** below the hymen - It is derived from the endoderm of the **urogenital sinus**.
- Vaginal canal is directed upwards and backwards forming an angle of **45° with the horizontal** in erect posture.
- The diameter of the canal is **2.5 cm** being widest at its upper part and narrowest at its introitus.
- Vagina is **H-shaped** in transverse section; length of **anterior wall** is about **8 cm** and **posterior wall** is about **10 cm**.
- There are 4 fornices - **anterior (shallowest)**, **posterior (deepest)** and two lateral.
- Vaginal epithelium is **non-keratinized stratified squamous** without **NO mucus secreting glands** (vaginal secretion is derived from endocervical and endometrial glands and Bartholin's glands).

- Vaginal **pH** is **acidic (4–5)** from puberty to menopause because of the **Doderlein's bacilli (gram positive lactobacilli)** that produce lactic acid from glycogen present in the exfoliated cells.
- **Before puberty** and **after menopause** the vaginal **pH** is about 7.
- For hormonal **cytology** (vaginal smears), the **lateral wall of the upper third of the vagina** is lightly scraped since this part is **most sensitive** to hormonal influence.
- **Relations**
 - Anteriorly: Bladder (upper 2/3) and urethra (lower 1/3).
 - Posteriorly: Rectouterine **Pouch** of Douglas (Upper 1/3); Ampulla of rectum (Middle 1/3); Perineal body (Lower 1/3).
 - Laterally:
 - **Mackenrodt's** ligament/Pelvic cellular tissue (upper 1/3);
 - **Levator ani** (middle 1/3);
 - **Bulbocavernosus**, vestibular **Bulb**, Bartholin's glands (lower 1/3).
 - '**Medicos Love Books!**'
 - The cervix and all 4 vaginal fornices are related to **Ureter, Uterine vessels** and **Mackenrodt's ligament**.
- **Blood Supply**
 - Vaginal artery (branch of anterior division of internal iliac artery or directly from uterine artery)
 - Cervicovaginal branch of uterine artery
 - Internal pudendal artery
 - Middle rectal artery
- **Veins** drain into internal iliac veins.
- **Nerve supply:** Upper vagina has sympathetic and parasympathetic (S2–4) innervation; lower part of vagina is supplied by **pudendal nerve**.
- **Lymphatics**—on each side drain into
 - Upper one-third and middle one-third up to hymen into internal iliac group
 - Below the hymen into superficial inguinal group.

Uterus

Uterus position/measurements

- **Normal position**
 - **AnteVersion:** Angle between long axis of cervix and Vagina = **90 degrees**
 - **Anteflexion:** Angle between long axis cervix and body of uterus = **120–130 degrees**
 - Uterus usually inclines to the right (**dextrorotated**) so that the **cervix** is directed to the left (**levorotated**) and comes in close relation with the **left ureter**

Contd...

Contd...

Uterus position/measurements

- **Measurements**
 - Uterus measures totally **8 cm long** (of this **cervix is 2.5 cm**) by **5 cm wide** and is **1.25 cm thick**
 - Weight of non-pregnant uterus = **50–80 grams** and of pregnant uterus = **1000 grams**
 - Length of pregnant uterus = **35 cm**
 - Capacity of non-pregnant uterus = 10 mL and of pregnant uterus = 5000 mL
- Uterus consists of **Body (corpus)**, **Isthmus** and **Cervix**. Superolaterally the body projects and is called **cornu** of the uterus.
- Structures attached to the cornu are: **Round ligament**; Fallopian **Tube** and **Ovarian ligament** (RTO).
- **Body** of uterus:
 - The three layers of body of uterus are inner endometrium, middle myometrium and outer perimetrium (serosa).
 - As there is **NO submucosal layer**, the endometrium is directly apposed to the myometrium.
 - **Endometrium** is the mucosa of the uterine cavity and is lined by **ciliated columnar** epithelium.
 - Myometrium has 3 layers: **outer longitudinal** smooth muscles, **middle criss-crossing** (figure-of-8) muscle fibers and **inner circular** muscle fibers. The **middle layer of myometrium** acts as a **living ligature** during involution of the uterus and prevents blood loss.
- **Isthmus** (0.5 cm) extends from **anatomical internal os above** (where **endometrial canal becomes cervical canal**) and to the **histological internal os below** (where **epithelium of uterus changes to epithelium of cervix**).
- **Cervix**
 - Supravaginal part (**endocervix**) is lined by **simple columnar** epithelium.
 - Vaginal part of cervix (**exocervix**) is lined by **stratified squamous nonkeratinized** epithelium.
 - The **squamocolumnar junction** of the cervix is situated at the **external os**.
 - **Corpus: cervix ratio** = Before puberty (1:2); At puberty (2:1); In adults/reproductive age (3:1).
 - Cervix is the most fixed part of the uterus.
- The peritoneum between the uterus and bladder forms the **utero-vesical pouch** and between the uterus and rectum forms the **rectouterine pouch (Pouch of Douglas)**. In the **upright** position, this is the **most dependent part** of the peritoneal cavity. In the supine position it is the most dependent part of the pelvic cavity.

- **Blood supply:**
 - **Uterine artery** (branch of **anterior division of internal iliac artery**) and ovarian artery.
 - Uterine veins drain into **internal iliac vein**.
- **Nerve supply:**
 - Sympathetic nerves are from T5 and T6 (motor) and T10 to L1 spinal segments (sensory)
 - Parasympathetic fibers (motor and sensory), S2, 3, 4 end in the ganglia of Frankenhauser.
- **Lymphatic drainage:**
 - From fundus and upper part of body: to pre-aortic and lateral aortic groups
 - From cornu: to superficial inguinal gland
 - From lower part of the body: to external iliac group
 - From cervix: to **IHOPE:** **I**nternal iliac, **H**ypogastric, **O**bturator **P**resacral (paracervical), **E**xternal iliac nodes.
- **Supports of the Uterus:** See table as follows:

Primary supports	
Muscular (active) supports	Fibromuscular (ligamentous) supports (mechanical supports)
<ul style="list-style-type: none">▪ Levator ani muscles of the pelvic diaphragm▪ Perineal body▪ Muscles of urogenital diaphragm, deep transverse perineal and sphincter urethrae muscles	<ul style="list-style-type: none">▪ Transverse cervical (cardinal, Mackerodt) ligament: contains uterine vessels▪ Round ligament of uterus▪ Pubocervical ligament▪ Uterosacral ligament
Secondary (doubtful) supports	
These are of doubtful value and are only folds of peritoneum	
<ul style="list-style-type: none">▪ Broad ligament▪ Uterovesical fold of peritoneum▪ Rectovaginal fold of peritoneum	

EXTRA EDGE

- At the lateral fornix of the vagina, the uterine artery crosses the ureter superiorly (called '**water under the bridge**'—with water depicting the ureter and uterine artery, the bridge) while clamping the uterine artery during hysterectomy, the ureter is in danger of being clamped.

Uterine (Fallopian) Tube

- Fallopian tube is present in **upper free margin** of broad ligament of uterus.
- It is **10 cm** long.
- It is lined by **ciliated columnar** epithelium; **secretory Peg cells** are also present in proximal part of the tube.
- Blood supply: from **uterine artery** (medial 2/3) and from **ovarian artery** (lateral 1/3).

- Lymphatic drainage: into **para-aortic** nodes.
- The 4 parts of Fallopian tube and their special characteristics are give in following table:

Part	Features
Intramural (interstitial)	1 cm long, shortest and narrowest part; lies in the uterine wall; acts as anatomic sphincter
Isthmus	3 cm long; acts as physiologic sphincter (due to circular smooth muscle and adrenergic innervation); MC site of ligation during tubal ligation
Ampulla	5 cm long; longest and widest part; Fertilization of ova takes place here, MC site of ectopic pregnancy
Infundibulum	Also called fimbrial end

Broad Ligament

- The broad ligament is a large peritoneal fold that attaches the uterus to the lateral pelvic wall.
- Subdivisions of the broad ligament and their contents (in turn, they are also **contents of broad ligament**) are:
 - **Mesovarium** - connects the posterior layer of broad ligament with anterior surface of ovary - contains ovarian blood vessels and nerve plexuses.
 - **Mesosalpinx** - fold of broad ligament that suspends the uterine tube-contains **uterine tube, round ligament of uterus, ligament of ovary, paroophoron** and **epoophoron**.
 - **Mesometrium** - extends from pelvic floor to the uterine body - contains **uterine vessels, uterovaginal nerve plexuses, duct of Gartner**.
 - **Suspensory ligament of ovary** (infundibulopelvic ligament) - contains **ovarian vessels**, lymphatic and nerve plexuses.

Ovary

- Ovary is an **intraperitoneal** structure lying in the **ovarian fossa** (of **Waldeyer**) on the **lateral pelvic wall**.
- **Ovarian fossa** is bounded
 - Anteriorly by the **obliterated umbilical artery**.
 - Posteriorly by the **ureter** and **internal iliac artery**.
 - **Floor (lateral surface)** of the ovarian fossa contains **obturator nerve** and vessels.
- **Ligaments of the ovary**
 - The **anterior border of the ovary** is attached to the posterior layer of the broad ligament by the **mesovarium**.
 - **Lateral part of the broad ligament** of uterus forms a distinct fold known as **suspensory ligament** of the

- ovary (infundibulopelvic ligament). It contains the **ovarian vessels and nerves**.
- **Ligament of ovary (ovarian ligament)** is a derivative of gubernaculum and connects the **lower pole** of the ovary to the **lateral angle** of the uterus.
- Note: The **posterior** border is the **free** border of the ovary.
- **Histology of ovary**
 - Ovary is lined by single layer of cubical cells known as germinal epithelium of Waldeyer.
 - Ovarian cortex has follicles in various stages of development.
 - Ovarian medulla contains '**hilus cells**' which are homologous to the **interstitial cells** of the testis; they are found **MC at pregnancy and at menopause**, but their function is unknown; tumors arising from these cells cause **masculinization**.
- **Nerve supply**
 - **Sympathetic** fibers arise from **preganglionic** fibers at the **T10/T11** level and **supply the ovaries and Fallopian tubes** through sympathetic fibers that follow the ovarian vessels.
 - Ovaries, (like the testes) are **sensitive** to manual squeezing. Ovarian pain can be referred to **periumbilical** (T10) region and to the **medial side of thigh** (distribution of obturator nerve)
 - **Intractable ovarian pain** maybe relieved by **cutting the suspensory ligament** which contains ovarian plexus.
- **Blood supply:**
 - **Ovarian artery** that arises from the **aorta** just below the renal artery.
 - **Right** ovarian vein drains into the **IVC**, while **left** ovarian vein drains into **left renal vein** (REMEMBER:

- venous drainage of right and left adrenals and testis is similar to this).
- **Lymphatic drainage** is into **para-aortic** (lateral aortic) nodes.

Sensitivity of Reproductive Organs

Cervix and uterus	Both are Insensitive to touch, grasping by any instrument; Uterus is insensitive even to incision over its wall
Fallopian tube	It is very sensitive to handling
Ovaries and testis	They are sensitive to manual squeezing

MENSTRUAL PHYSIOLOGY

Endometrium

Superficial 2/3	Deep 1/3
Stratum functionale (stratum compactum + spongiosum)	Stratum basalis
Supplied by spiral arteries which undergo vasoconstriction during secretory phase due to PGF-2alpha	This layer is in contact with myometrium and supplied by basal arteries which do NOT undergo vasoconstriction
This leads to necrosis and sloughing off of these layers during menstruation	This zone is NOT influenced by hormonal changes and remains intact. During secretory phase, it causes regeneration of entire endometrium

Menstrual Cycle

The menstrual cycle consists of the Ovarian Cycle and the Uterine (endometrial) cycle which occur parallelly as shown in the following table:

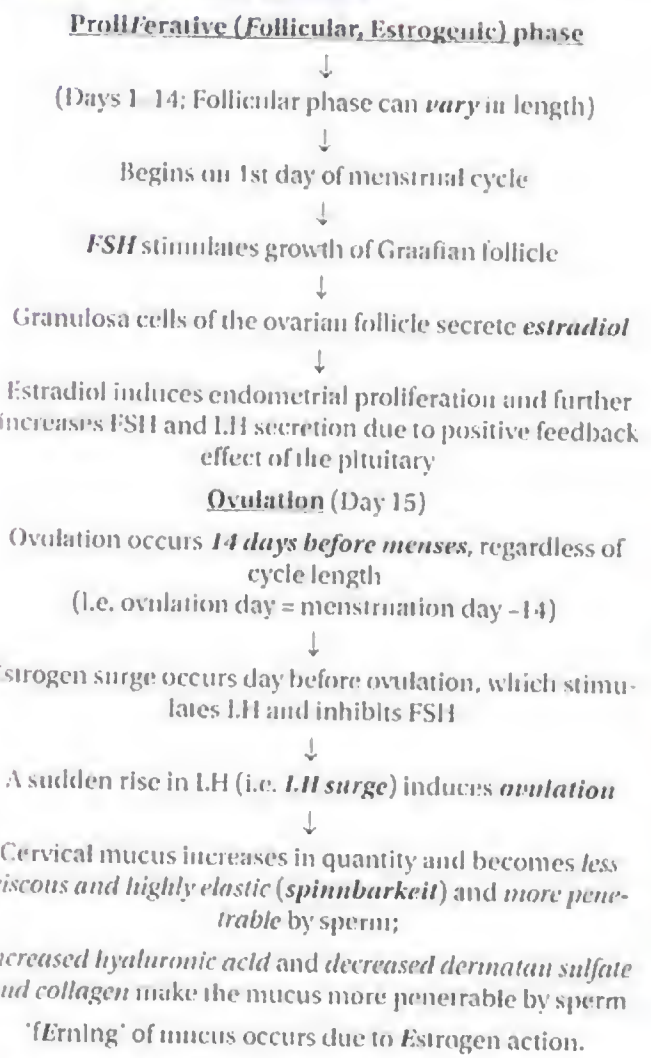
Ovarian Phase	Uterine (endometrial) phase	Events	Histology (endometrial biopsy)
Follicular phase (days 1-14); this phase can vary in length ; begins on first day of menstruation	Menstrual phase (days 1-5)	Low estrogen and progesterone levels causes withdrawal of hormonal support to the endometrium which causes necrosis and the endometrium is shed off	Stratum functionale and coiled arteries are absent
	Proliferative (Estrogenic) phase (days 6-14)	Dominated by estrogen effect that induces replacement of endometrial cells lost during menses	Stratum functionale is thin, endometrial glands are straight and arteries are less coiled

Contd...

Contd...

Ovarian Phase	Uterine (endometrial) phase	Events	Histology (endometrial biopsy)
Ovulation (Day 14)		LH surge induces ovulation	Subnuclear basal vacuolation is earliest evidence of ovulation
Luteal Phase (Days 15-28); (Luteal = Secretory. Endometrium is LOOTED !)	Secretory Phase (days 15-28)	Dominated by progesterone which along with estrogen prepares the endometrium for implantation	Saw-toothed endometrial glands (corkscrew shaped) and highly coiled spiraled arteries; Stromal edema

Overview of Menstrual Cycle



- **Mittelschmerz** ('pain of ovulation') - blood from ruptured follicle causes peritoneal irritation that can **mimic appendicitis**.
- OCPs prevent estrogen surge, LH surge (so ovulation does not occur).

Secretory (luteal, Progesterone) phase (Days 15-28, Luteal phase is usually a **constant** 14 days)

The residual follicle (i.e. corpus luteum) begins to develop and synthesizes estrogen and progesterone
➤ **Progesterone** stimulates endometrial glandular secretion and vascular development in anticipation of fertilized egg.
➤ **Basal body temperature** increases due to effect of **progesterone**.
If the ovum is not fertilized, the corpus luteum regresses, progesterone and estradiol levels decrease and endometrium is sloughed off (i.e. **menses**).

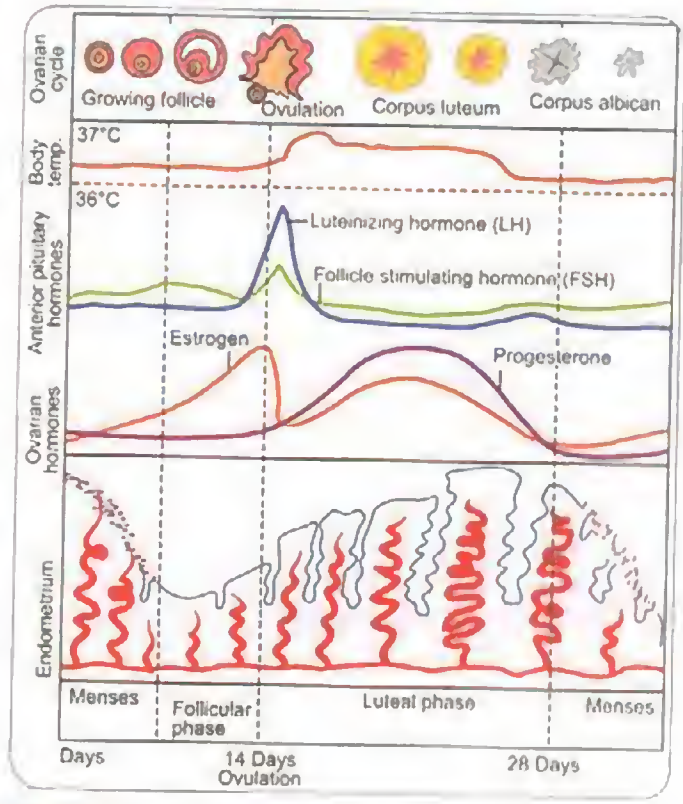


Fig. 25.2: Overview of menstrual cycle

Ultrasound Patterns of Endometrium

Phase	Pattern
Menstrual phase	Hyperechoic, Linear
Proliferative phase	HYPOechoic, 4–8 mm
Periovulatory phase	'Triple Line (trilaminar)' endometrium; 6–10 mm (characteristic of late proliferative phase)
Secretory phase	Hyperechoic, 7–14 mm
Postmenopause	Hyperechoic, thin < 5 mm
Postmenopause with hormone replacement therapy	Variable ultrasound patterns, 4–8 mm

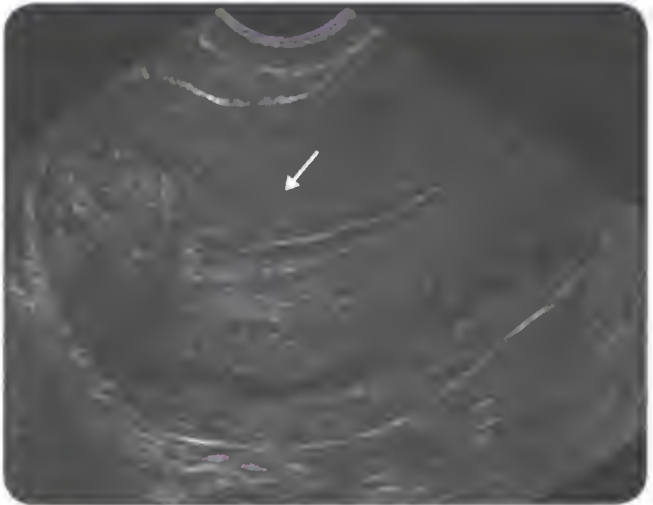


Fig. 25.3: USG appearance of endometrium at the time of ovulation

Ovarian Follicles

- Before puberty, all follicles in the ovary are in the primordial follicle stage. In **primordial follicles**, the oocyte is arrested in the last stage of prophase (known as **dictyotene** stage). This has been described under 'Oogenesis' in Embryology chapter.
- The **pulsatile release of GnRH** (LHRH) along with nonpulsatile release of **leptin** has a major role in initiation of puberty. Thus at puberty, further development of the primordial follicles occurs.
- Ovarian follicles mature through 4 developmental stages: **Primordial - Primary - Secondary - Graafian**.
- It is the **mature Graafian follicle** that undergoes **ovulation**.

- Just before ovulation, size of this Graafian follicle is **19–20 mm** with a volume of **3.5 mL**.
- **Follicular recruitment**: the process by which certain primordial ovarian follicles begin growing in a given menstrual cycle; recruitment of follicles is done by **FSH**, BUT Rupture of follicles is by **LH**.

Corpus Luteum

- After ovulation, the ruptured Graafian follicle collapses and fills with a blood clot (**corpus hemorrhagicum**), which then forms the **corpus luteum**. If pregnancy does not occur, then the corpus luteum degenerates into the **corpus albicans**.
- In non-pregnant state corpus luteum is maintained by **LH**; BUT in pregnancy state, it is maintained by **HCG**.
- Lifespan of corpus luteum is about **12–14 days**.
- **Luteal-placenta shift** is the turnover of function from corpus luteum of pregnancy to placenta. This transition period continues for 7–10 weeks; this is essential for growth of fertilized ovum.
- **Luteal-follicular shift** is the period that extends from demise of corpus luteum to the selection of a new dominant follicle for the next cycle.
- Corpus luteum is responsible for production of **estrogen and progesterone in first 2 months** of pregnancy.
- **Luteal phase defect**: refers to a condition where production of **progesterone is suboptimal** by the corpus luteum.

More One-Liners in Menstrual Physiology

- **Ovulation** occurs **32–36 hours (OR 24–36 hours)** after **LH surge** OR **10–12 hours after LH peak**, i.e. 75 ng/mL of LH.
- Menstrual blood is mainly **arterial blood**.
- **Prothrombin, free thrombin, fibrinogen and fibrin** are **absent** from menstrual blood.
- Release of **PGF-2alpha** at menstruation occurs due to withdrawal of progesterone; this PGF-2alpha causes myometrial contraction leading to pain during menstruation (dysmenorrhea); thus pain is always present during ovulatory cycles.
- The **spiral arteries** of the endometrium are converted to **large bore utero-placental arteries**.

Inhibin

- **Inhibin** (folliculostatin) a peptide from the ovary and testes (Sertoli cells mainly) selectively inhibits FSH release; dopamine inhibits only LH release.
- There are 2 forms - Inhibin A and Inhibin B.
- In both of them alpha-subunit is identical, BUT beta-subunit is specific.

	Inhibin A	Inhibin B
Secreted by	Secreted by corpus luteum in luteal phase under the effect of LH	Secreted by granulosa cells in proliferative phase under effect of FSH
Peak levels	Mid luteal phase	Mid follicular phase
During pregnancy	Placenta produces Inhibin A	Inhibin B levels are low

HORMONES

Gonadotropins (FSH and LH)

- **Natural gonadotropins** are **FSH and LH** produced by **basophil cells** of **anterior pituitary** in a **pulsatile** manner.
- T-1/2 of **FSH** = 3–4 hours; **LH** = 20 minutes.

	FSH (Follicle stimulating hormone)	LH (Luteinizing hormone)
In females	<ul style="list-style-type: none">• Induces follicular growth• Development of ovum• Estrogen secretion	<ul style="list-style-type: none">• Ovulation induction.• LH brings about luteinization of the ruptured follicle and thus forms and maintains corpus luteum till the next menstrual cycle in non-pregnant state.• Progesterone secretion
In males	<ul style="list-style-type: none">• It supports spermatogenesis and has a trophic influence on seminiferous tubules	<ul style="list-style-type: none">• LH stimulates testosterone secretion by the interstitial cells of Leydig and is called the interstitial cell-stimulating hormone

EXTRA EDGE

- MC used **synthetic** preparation of FSH and LH is **hMG** (human menopausal gonadotropin) obtained from urine of postmenopausal females; each ampoule contains 75U FSH and 75 ULH.
- FSH promotes **gametogenesis** both in males and females.

Gonadotropin Releasing Hormone (GnRH)

- Natural GnRH is a **decapeptide** synthesized by the **arcuate nucleus** of the hypothalamus and released **at puberty** in a pulsatile manner (**pulsatility** most important for puberty).
- **Leptin**, a hormone produced by **adipose cells**, plays a **permissive role** in the resurgence of GnRH secretion at the onset of puberty.
- GnRH pulse generator is regulated as follows:
 - **Stimulatory**: Glutamic acid, **kisspeptin** (regulates leptin), neurokinin B
 - **Inhibitory**: GABA; proenkephalin, dynorphin.

EXTRA EDGE

- **Kallmann syndrome**: **Congenital defective hypothalamic GnRH** synthesis and is a/w **anosmia** or hyposmia due to olfactory bulb agenesis or hypoplasia. Classically, the syndrome may also be a/w **color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism**, and neurologic abnormalities such as **mirror movements**. Leads to **delayed puberty, hypogonadism and primary amenorrhea** (in females).

GnRH Analogs/Agonists

- GnRH agonists have **longer half life (3–8 hrs)** and **greater potencies (15–200 times)**.
- **Flare effect**: Initially GnRH agonists stimulate anterior pituitary resulting in increased LH and FSH secretion.
- **Downregulation**: After 'flare' there is a decrease in synthesis and release of both FSH and LH.
- When given in pulsatile manner GnRH agonists stimulate gonadotropin secretion whereas on continued administration they inhibit gonadotropin release. Hence used in **pulsatile** manner for **ovulation induction and delayed puberty**.
- Also used for treating conditions a/w increased estrogen-**endometriosis, precocious puberty** and **fibroids**.
- Synthetic GnRH agonists are given by **intranasal** route.
- Examples: Buserelin, Goserelin, Leuprorelin, Nafarelin, Triptorelin, Historelin.
- **Adverse effects of GnRH agonists**: Menopausal like symptoms (hot flashes, vaginal dryness, osteoporosis, headache, depression, joint stiffness).

EXTRA EDGE

- **GnRH antagonists** act immediately to stop gonadotropin secretion without flare effect. BUT these have been surpassed by GnRH agonists in clinical practice EXCEPT for their potential role in **contraception** (Nal-Glu inhibits spermatogenesis).

Estrogen and Progesterone Compared

	Estrogen	Progesterone
Composition	C18 compounds <ul style="list-style-type: none">• E1- Estrone• E2 - 17-beta-Estradiol• E3 - Estriol	C21 compounds <ul style="list-style-type: none">• BUT <i>synthetic</i> progesterones are C18 compounds
Secreted from	<ul style="list-style-type: none">• Granulosa cells of follicles (E2)• Corpus luteum (E2)• Placenta (E3)	<ul style="list-style-type: none">• Corpus Luteum• Placenta
Receptor	<ul style="list-style-type: none">• Intranuclear	<ul style="list-style-type: none">• Intracytoplasmic
Circulating form	<ul style="list-style-type: none">• 60% bound to albumin• 38% bound to sex hormone binding globulin (SHBG)• 2% free	<ul style="list-style-type: none">• 80% bound to albumin• 18% bound to corticosteroid binding globulin• 2% free
Effects on female genitalia	<ul style="list-style-type: none">• Proliferation of endometrium• Growth of <i>non-pregnant</i> uterus• Increases motility and decreases secretion of Fallopian tubes• Clear, watery, copious cervical mucus secretion which is elastic (<i>spinnbarkeit</i>); when dried and seen under microscope-shows fern like pattern• Vagina: <i>Superficial</i> cells predominate with high karyopyknotic index	<ul style="list-style-type: none">• Secretory effect on endometrium (tortuous glands)• Growth of <i>pregnant</i> uterus• Decreased motility and increased secretion of Fallopian tubes• Scanty, thick cervical mucus• Vagina: <i>Intermediate</i> cells predominate and low karyo-pyknotic index
Secondary sexual characteristics	<ul style="list-style-type: none">• Enlargement of breasts (growth of ducts and stroma) - ductular development	<ul style="list-style-type: none">• Enlargement of breasts (lobules and alveoli) - glandular development
Other effects	<ul style="list-style-type: none">• ↓LDL; ↑HDL; ↑TG (Plasma cholesterol lowering action)• Salt and Water retention• Closure of Epiphysis• Promotes bone mineralization• Procoagulant	<ul style="list-style-type: none">• ↑LDL; ↓HDL; ↓TG• Thermogenic (raises basal body temperature by 0.2–0.5 °C)

More about Natural Estrogens

- **17-beta-estradiol (E2):**
 - E2 is the **most potent** natural estrogen
 - E2 is **main** form of estrogen during **reproductive years**.
- **Estrone (E1):**
 - E1 is only 1/10th as biologically active as E2.
 - E1 is the principal estrogen in **postmenopausal** females. Obese ladies have increased E1.
- **Estriol (E3):**
 - E3 is only 1/100th as active as E2.
 - It is produced by **placenta during pregnancy** and is the most specific estrogen during pregnancy.
 - It is also an indicator of **maternal-fetal well being**.
- **Mnemonic:** E1(**E-ONE**) = Estr**ONE**; E3 (3=**TRI**) = Est**TRI**ol
- Normally **E2:E1 = 2:1**; BUT in obesity/PCOD E2:E1 = 1:2.

- **Premarin** (conjugated equine estrogen) is obtained from urine of pregnant mares. Used orally or IM/IV injection.
- **Estradiol valerate** used for *priming endometrium* in donor oocyte program.

Synthetic Estrogens and Progesterones

Synthetic Estrogens	Synthetic Progesterones
<ul style="list-style-type: none">• Steroidal estrogens<ul style="list-style-type: none">– Ethinyl estradiol (MC used)– Mestranol• Non-steroidal estrogens<ul style="list-style-type: none">– Diethylstilbestrol– Hexestrol– Dienestrol	<ul style="list-style-type: none">• 1st generation (19-nortestosterone derivatives)<ul style="list-style-type: none">– Norethindrone– Norethynodrel– Norethisterone acetate• 2nd generation<ul style="list-style-type: none">– Levonorgestrel– Norethisterone– Norgestrel

Contd...

Contd...

Synthetic Estrogens	Synthetic Progesterones
	<ul style="list-style-type: none">• 3rd generation (least androgenic activity)<ul style="list-style-type: none">– Desogestrel– Gestodene– Norgestimate• 4th generation (anti-androgenic)<ul style="list-style-type: none">– Drospirenone– Dienogest

Uses of Estrogens

- Oral **contraception**
- **Vaginitis** - oral estrogen or cream
- **Delayed puberty:** for breast development
- Lactation suppression
- Intersex state: **Gonadal dysgenesis** (46,XY) or **Turner's syndrome** (45,XO): for growth of *secondary sexual characteristics*.
- **DUB**
- **Cervical mucus** hostility
- For hormone replacement therapy (**HRT**).

Uses of Progesterone

- Progesterone **challenge test** (in inv. of amenorrhea)
- Contraception (oral or injectable)
- **DUB**
- **Endometriosis**
- **Dysmenorrhea**
- **Luteal phase defect**
- **Endometrial hyperplasia**
- PMS (Premenstrual Syndrome)
- For **hormone replacement therapy** (HRT)
- For **postponement of menstruation**, 5mg Norethisterone (progesterone) TDS for 3 days before expected period and continued till need for postponement; bleeding occurs 48–72 hours after withdrawal.

Anti-Estrogens

These include the SERMs (Selective Estrogen Receptor Modulators) and Aromatase inhibitors discussed here.

SERMs

- Clomiphene citrate (Described in detail under infertility topic)
- Tamoxifen / Doloxifen / Toremifene:
 - Beneficial action on one (decreased resorption) and lipid profile BUT **increases risk** of endometrial ca and thromboembolism.

- **Used** in breast Ca
- Can cause **ovulation induction**.
- Raloxifene:
 - Increases bone mineral density (used for **osteoporosis**); better lipid profile; risk of endometrial and breast cancer are **reduced**.
 - Does **NOT** improve hot flashes or urogenital atrophy.
 - **NOT** used in ovulation induction.
 - Increased venous **thromboembolism**.
- Ormeloxifene
 - Used as non-hormonal OCP - Saheli (centchroman).

EXTRA EDGE

- **Fulvestrant** is a **selective estrogen receptor downregulator**. It has improved safety profile, faster onset and longer duration of action compared to SERMs. It is FDA approved for post menopausal women with **hormone receptor positive metastatic breast cancer** that has progressed despite anti-estrogen therapy.

Aromatase Inhibitors

- These **inhibit the enzyme aromatase** in the granulosa cells of ovarian follicles and thus suppress estrogen synthesis.
 - First Gen: **Aminoglutethimide**
 - Second Gen: **Letrozole**; Anastrozole; Fadrozole, Formestane, Forozole, Exemestane.
- **Letrozole** has been used for **ovulation induction**.
- Other aromatase inhibitors are primarily used for treatment of **breast cancer** in **postmenopausal** women.

Anti Progesterone (Mifepristone RU 486)

- Competitive **antagonist of progesterone receptors** that nullifies the effect of endogenous progesterone. Thus there is increased release of prostaglandins from endometrium leading to menstrual bleeding and termination of pregnancy.
- Uses
 - Therapeutic **abortion (MTP)**: used **upto 7 weeks**; tab 200 mg is given orally followed by Misoprostol (PGE1) 400 mcg oral or 800 mcg vaginal pessary.
 - **Emergency contraception**: on 27th day of the cycle (irrespective of day of intercourse), 10 mg tablet is given.
 - **Cervical ripening** and induction of labor.
 - **Uterine fibroids**: for shrinkage.
 - **Endometriosis**: to reduce pain and reduce spread.
 - **Ectopic pregnancy**: injection into unruptured sac is one of the medical managements.
 - **Cushing's syndrome**: as it blocks glucocorticoid receptors also!

EXTRA EDGE

- **Ulipristal:** Selective progesterone receptor modulator. It delays/ blocks ovulation and delays maturation of endometrium. Used for **emergency contraception** ('Ella'-not yet available in India).

Androgens in Females

- Androgens in females are produced by the adrenals, ovary and from peripheral conversion of estrogen (with help of enzyme **aromatase**).
- Circulating androgens in females include:
 - Androstenedione (**MC** androgen produced by ovary)
 - Testosterone (is converted to Dihydrotestosterone, the **most potent androgen** by 5-alpha-reductase in androgen sensitive tissues)
 - Dehydroepiandrosterone (DHEA)
 - **DHEA-S** (DHEA-Sulphate) - produced **exclusively by adrenals** and used to assess adrenal function.

Danazol

- 17-alpha-ethinyltestosterone derivative.
- Has weak **androgenic**, antiogonadotropic and progestational activity.
- Uses
 - Uterus conditions: **Endometriosis, DUB, Fibroid, Infertility**.
 - Breast conditions: **Cyclical mastalgia, Fibrocystic breast** disease.
 - In **males**: Precocious puberty, gynecomastia, improves libido.
 - Others: Hereditary **angioneurotic edema**.

Gestrinone

- 19-nortestosterone derivative.
- It has actions similar to danazol BUT longer half life (28 hours) - so used in bi-weekly doses.

D/D OF PRIMARY AMENORRHEA

Condition	Breast	Pubic hair	Gonads	Karyotype
Testicular feminization (Androgen insensitivity)	Normal	Absent	Vagina ends in blind pouch	46, XY
Turner's syndrome (gonadal dysgenesis)	Under-developed	Absent	Streak gonads	45, XO
Mayer-Rokitansky- Kuster- Hauser syndrome (Mullerian agenesis)	Normal	Normal	Absent uterus and vagina, normal ovary; A/w renal tract (30%) and skeletal abnormalities (15%)	46, XX; Normal female phenotype
Hypogonadotropic hypogonadism (+ anosmia = Kallman syndrome)	Absent	Delayed	Delayed puberty + micropenis in males; normal stature	46, XY or 46, XX

- Its side effects are milder and hence **preferred over danazol**.

Anti-Androgens

Drugs	Remarks
5-alpha-reductase inhibitors (Finasteride, Duasteride)	Dihydrotestosterone production is reduced - used in Rx of BPH, male pattern baldness and hirsutism
Androgen receptor inhibitors (Cyproterone acetate, flutamide)	Used for treating hirsutism
Spironolactone	Aldosterone receptor antagonist; Used for treating hirsutism
Steroid synthesis inhibitors (Ketoconazole)	Can cause gynecomastia; NOT routinely used for anti-androgenic indication

MENSTRUAL DISORDERS

Amenorrhea

- **Amenorrhea:** Absence of menstruation.
 - **Primary amenorrhea:** When menstruation fails to begin by the age of 14 or in the presence of well-developed secondary sexual characteristics, by the age of 16. MC cause of **primary amenorrhea** is **gonadal dysgenesis** due to chromosomal abnormalities {ALSO NOTE: MC cause of **primary ovarian failure** is **gonadal dysgenesis** (Turner's syndrome)}.
 - **Secondary amenorrhea:** Amenorrhea of 6 months or more in a woman with previous normal menstrual function in absence of pregnancy (since the MC cause of secondary amenorrhea is **pregnancy**).

EXTRA EDGE

Swyer syndrome (Pure gonadal XY dysgenesis)

- Karyotype is **46 XY** BUT due to **mutation in SRY gene**, fetus develops as female
- Has normal female reproductive tract (uterus) BUT gonads are dysgenetic - needs gonadectomy as soon as diagnosis is made (high risk 40% of gonadoblastoma and dysgerminoma)
- Phenotypically (externally) appear as **tall females**
- **Primary amenorrhea** and **delayed puberty** (secondary sexual characters, breasts)
- Treatment: Administration of estrogen to promote puberty and female sexual characteristics; they will need cyclical progesterone once withdrawal bleeds are established
- They are also **able to have children** with assisted reproductive techniques and ovum donation.

Dysmenorrhea

- **Dysmenorrhea:** Painful menstruation. It maybe:
 - **Primary** dysmenorrhea is not a/w any pelvic pathology. Occurs due to the prostaglandins released by progesterone in the endometrium.
 - **Congestive** dysmenorrhea presents as pelvic pain a few days before the menses begins. After the onset of menses, patient is relieved of pain.
 - **Spasmodic** dysmenorrhea presents as cramping pain most pronounced on the first and second day of menses.

Other Variations of Menstruation

- **Normal menstrual blood loss:** 50-80 mL and does not exceed 100 mL.
- **Menorrhagia:** The menstrual cycle is unaltered but the duration and quantity of menstrual loss is **increased**.
- **Polymenorrhea/Epimenorrhea:** The **menstrual cycle is reduced** from the normal of 28 days to a cycle of 2-3 weeks and remains constant at that frequency.
- **Metrorrhagia:** **Irregular acyclical bleeding** from the genital tract. Bleeding may be intermittent or continuous.
- **Oligomenorrhea:** **Infrequent menses**. In this condition, the cycle length is prolonged (> 35 days) without affecting the duration and amount of flow.
- **Hypomenorrhea:** **Cycle length remains unaltered;** however the duration of bleeding or the amount of loss are both substantially reduced (< 2 days).

Benefits and Risks of HRT

Benefits	Uncertain risk	Definite risk	Uncertain benefits
<ul style="list-style-type: none">• Decreased hip, wrist, vertebral fractures• Symptoms of menopause improved	<ul style="list-style-type: none">• Thrombo-embolic events (use of E + P, not E alone)• Dementia• Endometrial cancer (use of E alone)	<ul style="list-style-type: none">• Coronary Heart disease• Breast cancer• Stroke• Cholecystitis• Ovarian cancer (E + P)	<ul style="list-style-type: none">• Reduction in colorectal cancer and diabetes mellitus

- **Cryptomenorrhea:** Occurrence of menstrual symptoms without external bleeding (occurs in **imperforate hymen**).
- **Precocious menstruation:** Menstruation starting before the age of **10**.

MENOPAUSE

- Menopause means **permanent cessation of menstruation** at the end of reproductive life due to **ovarian follicular inactivity** and **stoppage of estrogen** production.
- Average age of onset = **50 years** (earlier in smokers).
- **Premature menopause:** occurs before the age of **40 years**.
- **Late menopause:** menopause fails to occur even by **55 years**.
- Clinical features: **Hot flashes, Atrophy of Vagina, Osteoporosis, Coronary artery disease, ('HAVOC')**.
- **Hormonal changes** = ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.
- Diagnosis:
 - MC symptom of menopause is '**hot flash**'.
 - **Elevated FSH levels > 40 mIU/mL** - **diagnostic** of menopause; postmenopausal levels are 50-100 mIU/mL.
 - **Serum estradiol < 20 pg/mL**.
 - **Vaginal cytology** showing maturation index of at least 10/85/5.

Treatment: Hormone Replacement Therapy (HRT)

- For **woman with intact uterus**: progestin + estrogen.
- For **postmenopausal woman who has had hysterectomy**: estrogen without a progestin.
- **Tibolone** (STEAR - Selective Tissue Estrogen Activity Regulator) useful for **hot flashes and osteoporosis**.
- **Raloxifene** (SERM - Selective Estrogen Receptor Modulator) useful for **osteoporosis**.
- Estrogen maybe given orally, transdermally and as a vaginal cream.
- **Absolute contraindications** for HRT are:
 - Active liver disease/gallbladder disease
 - Undiagnosed vaginal bleeding
 - Cancers (endometrial uterine)
 - DVT (deep vein thrombosis)

Other Non-hormonal Treatments

- **For hot flashes:** Clonidine; SSRIs (paroxetine, venlafaxine); GABA-pentene; Dopamine antagonist (Veralipride); Soy protein; Vitamin E.
- **For osteoporosis:** Bisphosphonates; Calcium, Calcitonin, Vitamin D, etc. [complete treatment of osteoporosis including *teriparatide*, *denosumab* and *strontium ranelate* has been discussed in orthopedics chapter (Pg 743)].

CONGENITAL ABNORMALITIES OF FEMALE GENITAL ORGANS

Imperforate Hymen

- It is due to failure of disintegration of the central cells of the Mullerian eminence that projects into the urogenital sinus.

Menstrual blood collects behind the hymen
(*cryptomenorrhea*)

↓
Vagina gets distended (*hematocolpos*)

↓
Uterine cavity gets dilated (*hematometra*)

↓
In late and neglected cases, the fallopian tube may also be distended after the fimbrial ends are closed by adhesions (*hematosalpinx*)

- **Diagnosis:** A girl aged **14–16 years** presents with **lower abdominal pain** with **primary amenorrhea** and **retention of urine** (due to *elongation of urethra*).
- **Treatment:** **Cruciate incision** in the hymen with partial excision of the quadrants; pressure from above should NOT be given; internal examination should not be done.

Mullerian Agenesis

- Mullerian agenesis = *Complete agenesis of vagina (vaginal atresia) + absent uterus*
- Mullerian agenesis + **renal** anomalies and **skeletal** anomalies = **Mayer Rokitansky Kuster Hauser syndrome**.
- Patients is **phenotypically female** with normal female karyotype (**46 XY**).
- **Healthy ovaries** and **Fallopian tubes** are present - hence oocyte can be picked up and used for IVF - thus these females can have children.
- **Treatment** of vaginal agenesis/atresia: **to enable coitus**; menstruation is NOT possible.
 - **Frank and Ingram procedure:** Non-surgical procedure: A vagina can be created using serial vaginal di-

lators pressed into the perineal body— this can take from 4 months to several years.

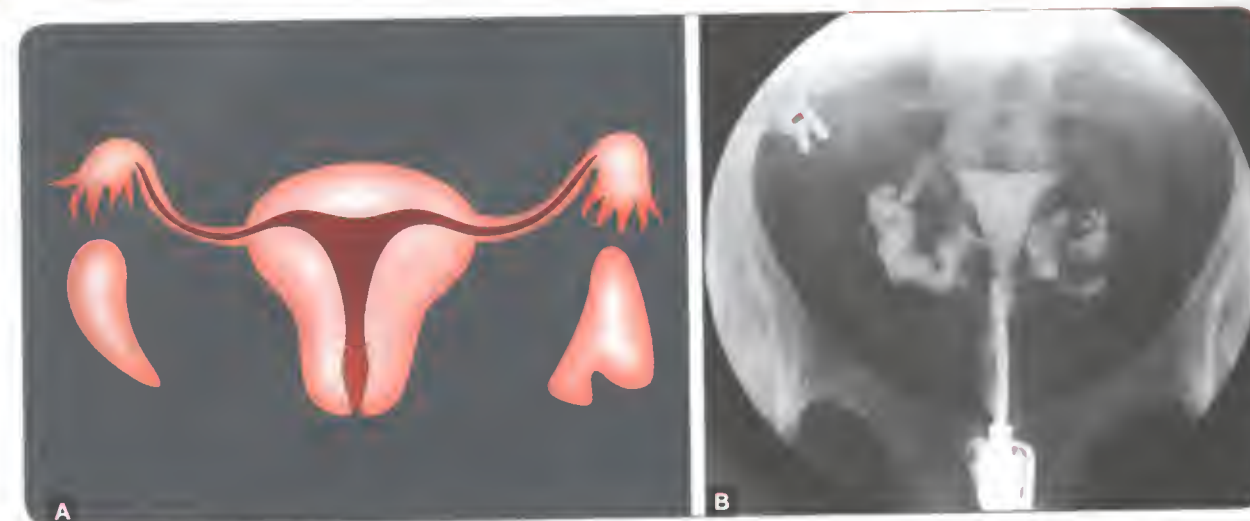
- **Vaginoplasty:** *William's or McIndoe (most popular)* or bowel or amnion graft vaginoplasty.
- **Laparoscopically:** modified Vecchietti's operation.

Uterine Anomalies

- Failure of fusion of Mullerian ducts leads to uterine anomalies as below:
 - **Septate uterus (MC, 35%)**
 - **Bicornuate uterus**
 - **Arcuate uterus**
 - **Uterus unicornis** (failure of development of one Mullerian duct)
 - **Uterus didelphys** (complete **lack of fusion of Mullerian ducts** with a **double uterus, double cervix and double vagina**)
- **Clinical Features:**
 - **Gynecological:** *Infertility, dyspareunia, dysmenorrhea* and menstrual disorders.
 - **Obstetric:** *Midtrimester miscarriage*; Rudimentary horn (*ectopic*) pregnancy; cervical incompetence; increased *malpresentation*.
- **Reproductive outcome:** *Better obstetric outcome in septate uterus (86%) and bicornuate uterus (50%) is present; Unicornuate uterus has very poor pregnancy outcome.*
- **Treatment:**
 - Rudimentary horn should be excised.
 - Bicornuate or septate uterus - unification operations:
 - Abdominal metroplasty (*Tomkin's, Jones and Strassman procedures*)
 - **Hysteroscopic metroplasty** (MC done and **high success rate** of 80–90%).

Congenital Cysts

Vaginal Cyst	Vulvar cyst
<ul style="list-style-type: none"> • Epidermal inclusion (sebaceous) cyst • Mullerian cyst • Gartner duct cyst (mesonephric/Wolffian remnant) • Adenosis (mucus inclusions) • Endometriotic cyst • Vaginitis • emphysematosum 	<ul style="list-style-type: none"> • Epidermal inclusion (sebaceous) cyst • Bartholin (greater vestibular) gland cyst • Skene (paraurethral) gland cyst • Cyst of the canal of Nuck (hydrocele) • Leiomyoma • Urethral diverticulum



Figs. 25.4A and B: A. Hysterosalpingogram; B. Showing a normal hysterosalpingogram



Fig. 25.5: Showing bicornuate uterus on hysterosalpingograph

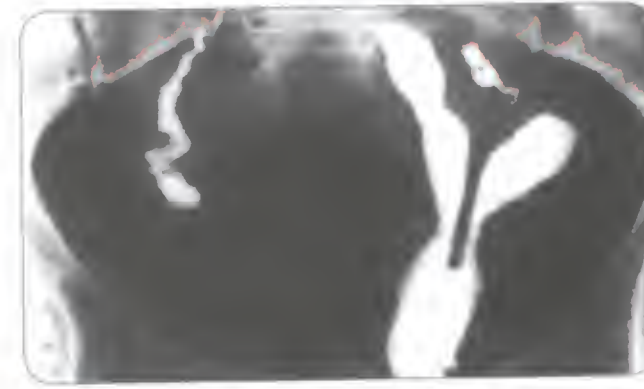


Fig. 25.6: hSG of septate uterus

VULVOVAGINAL INFECTIONS

Candidal Vulvovaginitis

- **Caused by *Candida albicans***, which flourishes in an **acid medium** with an **abundant supply of carbohydrate**.
- It is therefore common in **pregnancy, diabetes, use of OCPs, systemic steroids, antibiotics**.
- Clinically thick, white, **curdy discharge** with **extreme vulvar itching**; **White patches** of cheesy material adherent to the vagina which when removed, leave multiple petechial like hemorrhagic areas. (Candida = Curdy and remember Candida lesions anywhere in the body are always white!)
- **Diagnosis** is by microscopic examination of the vaginal discharge in **10% KOH** solution, which reveals candidal hyphae and buds.
- Cultures with **Nickerson's medium** may be used.

- Treatment is by **antifungal** agents: topical (**azole creams**) and/or systemic (**fluconazole**).

Trichomonas Vaginalis

- Trichomonas is actively motile and anaerobic.
- **Sexually transmissible**; its ingress into the vagina is favored when the **pH is raised (5–6) as during a menstrual period**.
- It is characterized by **copious, green, frothy discharge**, which may be associated with **foul odor and vulvar pruritus**.
- On examination **punctuation on the cervix**, classically called '**strawberry cervix**' is seen. ('**TRichomonas STRawberry**').
- **Diagnosis** may be made by saline wet mount of the vaginal discharge, which reveals highly **motile trichomonads**.
- Treatment is by **metronidazole**.

Bacterial Vaginosis

- This is caused by an overgrowth of a variety of bacterial species such as *Gardnerella vaginalis* (MC), *Bacteroides*, *Peptostreptococcus* and *Mycoplasma hominis* - polymicrobial.
- *Gardnerella vaginalis* vaginitis is characterized by vaginal discharge with a 'fishy/musty' odor with little vulvar irritation.
- **Amsel criteria:** any 3 of the following 4:
 - Increased **white homogeneous, thin watery vaginal discharge**;
 - A vaginal discharge **pH of >4.5**;
 - **Fishy odor** (due to volatile amines such as trimethylamine) immediately after vaginal secretions are mixed with a 10% KOH (**Whiff Test**).
 - Microscopic demonstration of '**clue cells**' (vaginal epithelial cells coated with coccobacilli) on a wet mount prepared by mixing vaginal secretions with normal saline in a ratio of ~1:1. Presence of **clue cells > 20%** is diagnostic of bacterial vaginosis.
- Treatment is by **metronidazole**.
- Mnemonic: 'There's something fishy, u need clues to detect Bad Villains (Bacterial Vaginosis)'

Herpes Genitalis

- Caused **MC by HSV 2** (90%) and by HSV 1 (10%). **Recurrent** infections are MC with **HSV 2**.
- **Sexually transmitted** and symptoms appear within 7 days of sexual contact.
- Red **painful** inflammatory vesicles and ulcers in the genital area with inguinal **lymphadenopathy** - HSV is the **MC cause of genital ulcers**.
- **PCR** to identify HSV DNA is most specific and accurate test.
- Adverse effects in primary infection in pregnancy
 - Increased risk of **miscarriage** and **preterm labor**.
 - Transfer of infection to neonate during vaginal delivery - delivery by **Cesarean section** is indicated with primary genital herpes at the time of delivery.
- Treatment: **Acyclovir** or **valcyclovir**.

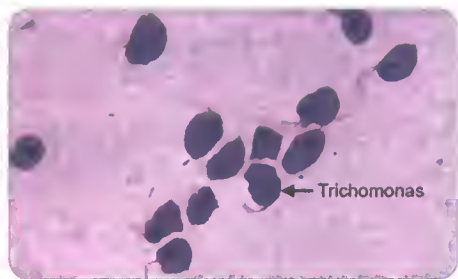


Fig. 25.7: Microscopic picture of trichomonas vaginalis showing trichomonas (arrow)



Fig. 25.8: Trichomoniasis: Strawberry cervix

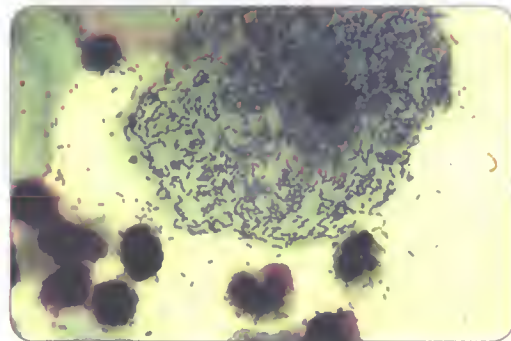


Fig. 25.9: Clue cells seen in bacterial vaginosis

PELVIC INFLAMMATORY DISEASE

- **Definition:** Infection or inflammation of the upper genital tract including ovary (oophoritis), fallopian tubes (salpingitis) and uterus (endometritis); (Note: Cervicitis and vaginitis are **NOT** included under PID).
- **Etiology:** Acute PID is **polymicrobial**
 - **Primary** organisms: sexually transmitted and include **Chlamydia (MC)**; **Gonococci** and **Mycoplasma**.
 - **Secondary** organisms: include **normal flora** of the vagina - *E. coli*, group B *streptococcus*, *Klebsiella* and anaerobes.
- **MC route of spread** of PID is **ascending infection** along with sperms (the only PID which does NOT spread this way is **genital TB** which has a **hematogenous** spread).
- **Pathology:**
 - PID is almost synonymous with **salpingitis** since the Fallopian tubes bear the brunt of acute infection.
 - The infection begins in the **endosalpinx**.
 - **Surest sign of salpingitis** is pus extruding from fimbrial end of the tube.
 - **Fitz Hugh Curtis** syndrome: PID + Perihepatitis In Chlamydial infection; **violin string adhesions** form between liver capsule and the peritoneum.

Clinical Diagnostic Criteria for PID (CDC 2010)

Minimum Criteria	Additional Criteria	Definitive Criteria
<ul style="list-style-type: none">• Lower abdominal tenderness• Adnexal tenderness• Cervical motion tenderness	<ul style="list-style-type: none">• Oral temp > 38.6°C (101.6°F)• Mucopurulent cervical or vaginal discharge• Abundant WBCs on saline microscopy of cervical secretions• Raised C-reactive protein and/or ESR• Lab documentation of positive cervical infection with Gonorrhea or Chlamydia	<ul style="list-style-type: none">• Histopath evidence of endometritis on biopsy• Imaging study (TVS/MRI) evidence of thickened fluid filled tubes +/- tubo-ovarian complex• Laparoscopic evidence of PID

Laparoscopic findings and severity of PID

- **Gold standard** for diagnosis of PID is **laparoscopy**.
- Laparoscopic findings and severity of PID is as follows:
 - **Mild:** Tubal edema, erythema, no purulent exudates and are mobile.
 - **Moderate:** Purulent exudates from fimbrial end; tubes NOT freely mobile.
 - **Severe:** Pyosalpinx, inflammatory complex, abscess.

Complications of PID

- Peritonitis
- Septicemia
- Dyspareunia
- Infertility
- Increased risk of ectopic pregnancy
- Chronic pelvic pain

Outpatient Treatment of PID (CDC 2010)

- Ceftriaxone 250 mg IM single dose
- Doxycycline 100 mg PO bid for 14 days with or without
- Metronidazole, 500 mg PO bid for 14 days

Indications or Hospitalization in PID

- Severe illness, vomiting, fever > 38 °C
- Suspected tubo-ovarian abscess
- Co-existing pregnancy
- HIV positive patient
- Unresponsive to OPD therapy for 48 hours.
- Uncertain diagnosis (e.g. appendicitis cannot be excluded)

Inpatient Antibiotic Therapy in PID (CDC 2006)

- Regimen A: Cefoxitin IV + Doxycycline PO.
- Regimen B: Clindamycin IV + Gentamicin IV.
- Alternative regimen: Ampicillin sulbactam IV + Doxycycline PO.

Genital Tuberculosis

- Genital TB is almost always **secondary to pulmonary TB**
- Pelvic organs are involved **MC** by **hematogenous** spread.
- MC site affected in genital TB is the **Fallopian tube** (90–100%) > **Uterus (Endometrium, 50–60%, second MC site)** > Ovary > Vagina and vulva.
- TB salpingitis:
 - **Both** tubes are affected **simultaneously**; abdominal ostium usually remains **patent**.
 - The initial site of infection is in the submucosal layer (**interstitial salpingitis**) of the **ampullary part** of the tube.
 - MC pathology is **endosalpingitis**
 - **Salpingitis isthmica nodosa** is the nodular thickening of the tube due to proliferation of tubal epithelium within the hypertrophied myosalpinx (muscle layer); this is also seen in **pelvic endometriosis**.
- MC age group affected is **20–30 years**; MC symptom is **infertility (70–80%)**.
- Treatment: ATT (anti-tubercular therapy); Surgery.

HSG findings suggestive of TB salpingitis are

- Vascular or lymphatic **extravasation** of dye
- Rigid (**lead pipe**) tubes with nodulations at places
- **Beading** and variation in filling density
- **Calcification** of the tube
- Bilateral **cornual block**
- Tubal diverticula and/or a **jagged fluffiness** of tubal outline
- **Tobacco pouch** and dilated distal end of the tubes due to hydrosalpinx and pyosalpinx
- Uterine cavity: irregular outline, honeycomb appearance or presence of uterine synechiae

EXTRA EDGE

- HSG is **contraindicated** in confirmed cases of genital TB due to fear of reactivation and spread of disease; BUT HSG is routinely done to detect causes of infertility and the above mentioned signs maybe seen in pelvic TB.

More about Asherman Syndrome:

- Etiology:** D & C (MC cause); TB; Pelvic infection
- Partial or complete obliteration of the uterine cavity by adhesions that prevent normal growth and shedding of the endometrium.
- Clinically:** Infertility; Amenorrhea; Hypomenorrhea; Recurrent pregnancy loss; cyclic pelvic pain.
- Diagnosis:** Gold standard is direct visualisation by hysteroscopy.
- Treatment:** By hysteroscopic lysis of adhesions and removal of scar tissue.

DISPLACEMENTS OF THE UTERUS

- Protrusion of pelvic organs into or out of the vaginal canal is called prolapse. External os lies at the level of ischial spine and internal os at the level of upper border of pubic symphysis. Hence any descent below these levels is called **prolapse**.
- The supports of the uterus have been discussed under anatomy in the beginning of this chapter.
- De-Lancey's** classifications of three levels is for supports of the vagina.
- Etiology:
 - **Acquired** prolapse: Repeated childbirth; menopause; traumatic deliveries; faulty birth practices; precipitate labor; iatrogenic (vaginal hysterectomy); increased intra-abdominal pressure (COPD, obesity, constipation).
 - **Congenital** prolapse (occurrence of prolapse in young **nulliparous** female): Spina bifida occulta; systemic disorders (Ehlers-Danlos syndrome, Marfan's syndrome). There is usually **NO cystocele** here.

Classification of Vaginal Prolapse

Anterior vaginal wall	Posterior vaginal wall
<ul style="list-style-type: none"> Upper 2/3: cystocele/ cystourethrocele Lower 1/3: Urethrocele 	<ul style="list-style-type: none"> Upper 1/3: Enterocoele (Pouch of Douglas herniates) Middle 1/3: Rectocele Lower 1/3: Lax perineum

Classification of Uterine Prolapse

Clinical classification (old)	Pelvic Organ Prolapse-Quantitative, POP-Q classification (new)
<ul style="list-style-type: none"> I degree: Descent of cervix to the vagina (external os still remains above introitus) II degree: Descent of cervix to the introitus (uterine body remains inside vagina) III degree (Procidentia): Descent of cervix outside the introitus, i.e. the cervix, body and fundus of uterus lies outside the introitus. 	<ul style="list-style-type: none"> Leading edge of Prolapse (LOP) in relation to distance from the hymen Stage 0: No descent of pelvic organs Stage 1: LOP > 1 cm above the hymen Stage 2: LOP ≤ 1 cm proximal or distal to hymen Stage 3: LOP > 1 cm below the hymen but protrudes no further than 2 cm less than total length of vagina Stage 4: Essentially complete eversion of vagina

- MC symptom** is that the patient feels something coming down or out of the vagina.
- Groin pain and **back pain** (due to **stretching of uterosacral** ligaments).
- Decubitus ulcer**—on the most dependent part of uterus/vagina - occurs due to **venous congestion and circulatory changes** (NOT due to trauma/friction). Treated by reduction of prolapse and packing with **glycerine and acriflavine**.
- Urinary** incontinence, frequency or urgency maybe seen.
- Ca cervix** - is a rare complication.

Treatment of Vaginal Prolapse

- Anterior **colporrhaphy**: for repair of cystocele and urethrocele
- Posterior **colpoperineorrhaphy**: for repair of lax perineum and rectocele
- Repair of enterocele**: Abdominal repair (**Moscowlitz** repair) or vaginal repair (**McCall** culdoplasty).

Treatment of Uterine Prolapse

- Abdominal sling operations
 - Suitable for - **young women with nulliparous prolapse** (second degree or more advanced uterovaginal prolapse); childbearing and menstrual functions are retained.
 - Examples are **Purandare's sling cervicopexy**; **Shirodkar's** sling and **Composite Virkud** Sling.

- Manchester operation (Fothergill's repair):**
 - Suitable for **women < 40 years** desirous of retaining menstrual functions, but does NOT desire future pregnancy.
 - Steps of Fothergill's operation are:
 - Preliminary D and C
 - Amputation of Cervix
 - Plication of Mackenrodt's ligaments in front of cervix
 - Anterior colporrhaphy
 - Colpoperineorrhaphy
- Vaginal hysterectomy** with pelvic floor repair (**Ward mayo's** operation):
 - Suitable for **women > 40 years** who have completed their families and do NOT desire menstrual and childbearing functions.
- Le Fort's repair:**
 - Suitable for **elderly menopausal patient > 60 years** who are medially unfit for hysterectomy.
- Pessary treatment:**
 - Use of **ring pessary** is nearly a history of the past when majority of elderly women and very young women desirous of childbirth received this treatment.

- Current indications for use of pessary are

- Prolapse during early **pregnancy or puerperium**
- Temporary use while clearing infection and decubitus ulcer
- Woman unfit for surgery/woman refusing surgery.

Vault Prolapse

- Vault prolapse** refers to prolapse of the **vaginal stump** left behind **after performing hysterectomy**
- It is accompanied by **enterocele** in 70% cases.
- Transabdominal **sacral colpopexy (uterosacral suspension)** is the **gold standard** surgery for vault prolapse.

EXTRA EDGE

- Kegel's exercises:** Pelvic muscle training exercises (by contracting and relaxing the muscles of pelvic floor) is a simple, noninvasive intervention that may improve pelvic function that has clearly demonstrated benefit for women with urinary or fecal symptoms, especially **incontinence**. It is started in pregnant females in **first trimester**; following vaginal delivery or cesarean section it can be started after **24 hours**.

GENITO-URINARY FISTULAE

	Vesico-vaginal fistula (VVF)	Uretero-vaginal fistula	Urethro-vaginal fistula
Etiology	Obstructed labor and ischemic necrosis (MC in developing countries) In developed countries hysterectomy	MC after injury to ureter in gynecological surgery-MC, Wertheim's hysterectomy	
Main symptom	Continuous dribbling of urine from vagina + NO normal urge for urination	Continuous dribbling of urine from vagina + NORMAL urge for urination	NO continuous leakage; BUT when patient urinates, urine leaks BOTH from urethra and vagina
Observation on Methylene blue swab test	Upper and lower swab remain dry BUT middle swab is stained with dye	Uppermost swab soaked with urine but NOT stained by dye (lower two swabs remain dry)	Upper two swabs remain dry BUT lowermost swab is stained with dye
Investigation	Cystoscopy	Cystoscopy Indigo carmine dye test	
Surgery	Latzko repair in layers Chassar Moir technique (for post hysterectomy VVF repair)	Boari flap technique	

Timing of Surgery in VVF

- If due to **obstructed labor** - repair after **3 months**
- If **iatrogenic (surgical)** and
 - If recognized within 24 hours - **immediate** repair
 - If recognized later - repair at **10-12 weeks**
- Radiation fistulas** are repaired after **12 months**.

Methylene Blue 3 Swab Test

- Used to differentiate between the different types of urinary fistulas
- A red rubber catheter is introduced into the bladder through the urethra.
- 3 cotton swabs are placed in the vagina as follows: one at vault; one at the middle; one just above the introitus.

- Methylene blue is instilled into the bladder through the catheter and the swabs are removed for inspection.
- Observation on methylene blue swab test is given in table above.

EXTRA EDGE

- **Mensouria:** Seen in **ureterovesical** fistula; usually follows **cesarean section**; **cyclical hematuria** occurs, i.e. blood/ menstrual matter is passed along with urine during time of menstruation; NO urinary incontinence occurs; treat by abdominal repair. ALSO KNOW: cyclical hematuria also occurs in **endometriosis of bladder**.

'Most Common' in Fistulae

Most Common (MC)	Comment
MC genitourinary fistula	Vesicovaginal fistula
MC cause of VVF in India	Obstructed labor
MC cause of uretero-vaginal fistula	Injury to ureter after gynecological surgery (MC Wertheim's hysterectomy)
MC cause of vesico-uterine fistula	Cesarean section
MC cause of recto-vaginal fistula	Obstetric trauma (prolonged II stage of labor with necrosis of rectovaginal septum); II MC cause is Crohn's disease

URINARY INCONTINENCE

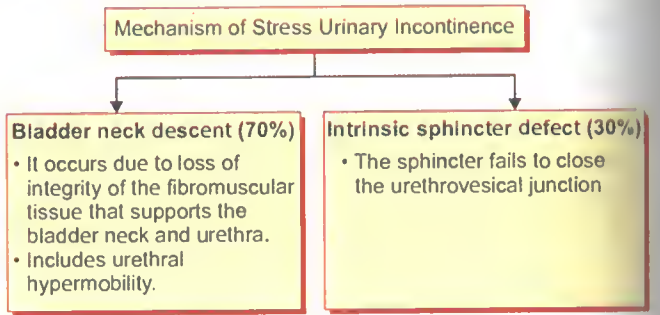
- **Definition:** Involuntary leakage of urine which is a social or hygienic problem to the patient.
- Physiology of micturition has been discussed in *physiology chapter (Pg 89)*.

Types of Urinary Incontinence

Stress Urinary Incontinence (SUI)	Urge Urinary Incontinence	Functional incontinence
Incontinence occurs when intra-abdominal pressure is increased as in sneezing/coughing/laughing	Incontinence occurs accompanied by or immediately preceded by the urge to void	Incontinence a/w cognitive, psychological or physical impairment that makes it difficult to reach the toilet
MC type of urinary incontinence in women. Mechanism is on next page.	Due to involuntary detrusor muscle contractions (MC Idiopathic)	Due to Delirium, Infections, Atrophy of sphincter; Pharmacological drugs; Endourinopathy; Restricted mobility; Stool impaction (DIAPERS!)

- **Mixed** incontinence: Both SUI and urge incontinence occurring together.
- **Bypass** incontinence: maybe caused by urogenital fistula or any congenital urinary tract abnormality.

Mechanism of Stress Urinary Incontinence



Tests for Detecting Incontinence

- **Bonney's test**
- **Marchetti test**
- **Q tip test**

Treatment of SUI

- First line: pelvic floor exercises: Kegel's exercises.
- Definitive treatment: Surgery

Current concept surgeries	Earlier surgery: Colposuspension
<ul style="list-style-type: none">▪ Minimally invasive synthetic midurethral slings (TVT or TOT)▪ TVT: Tension free Vaginal Tape▪ TOT: Tension free Obturator Tape▪ In both above surgeries, midurethra is suspended; both are vaginal surgeries and day care surgeries	<ul style="list-style-type: none">• Both are abdominal route surgeries• Burch colposuspension (proximal urethra is suspended to Cooper's ligament) - was considered gold standard procedure for SUI• Marshall Marchetti Krantz surgery (MMK) (proximal urethra is suspended to pubic symphysis - caused osteitis pubis - hence NO longer used)

EXTRA EDGE

- **Kelly's plication suture:** as the standard treatment earlier for SUI. Its cure rates are low and hence NO longer used.
- **Urge incontinence:** MC cause is **idiopathic**; other causes are mainly **neurologic** (Alzheimer's, Parkinson's, MS, CVA, etc.). Best treated by behavior therapy and **anticholinergic** drugs (to **reduce detrusor over-activity**).

DYSFUNCTIONAL UTERINE BLEEDING (DUB)

Anovulatory DUB (MC, 80%)	Ovulatory DUB (20%)
<ul style="list-style-type: none">▪ Threshold bleeding of puberty menorrhagia▪ Metropathia hemorrhagica (cystic glandular hyperplasia)▪ Premenopausal DUB (endometrial atrophy)	<ul style="list-style-type: none">▪ Irregular ripening of corpus luteum▪ Irregular shedding of corpus luteum (Halban's disease)▪ IUCD insertion▪ Following sterilization operation

Mechanism of Anovulatory DUB

- In anovulatory DUB, since there is NO ovulation, progesterone is low, BUT estrogen is normal and this proliferates the endometrium (hyperplasia) which eventually sheds off causing DUB.

Metropathia hemorrhagica

- **Cystic glandular hyperplasia** is seen in **metropathia hemorrhagica**.
- Metropathia hemorrhagica should be regarded as a specialized form of dysfunctional uterine bleeding.
- MC in women between 40 and 45 years of age.
- Symptoms are typical. A short period of **amenorrhea** followed by continuous **vaginal bleeding**, a period of 8 weeks elapsing between the last period and the onset of continuous hemorrhage.
- Pathologically, the endometrium shows cystic glandular hyperplasia - many of the glands show cystic dilatation and large cysts can be identified with naked eye. **Swiss cheese pattern** is another name given to this type of endometrium.

Treatment of Anovulatory DUB

- **Progesterone therapy** is the mainstay of treatment. Progestins act as powerful anti-estrogen, but it can act only on endometrium that has been primed by estrogen. Hence progesterone is given in the latter 12-14 days of the cycle. Drugs used are:

Status	Drug of choice
DUB in young girls who are not sexually active	Cyclical Medroxyprogesterone acetate: 5-10 mg in last 12-14 days of cycle
In sexually active women with DUB who also want contraception	OCPs (Estroegn + progesterone) OR DMPA injection (150 mg every 3 months): DOC.

Treatment of Ovulatory DUB

- **NSAIDs (Drug of choice)**
- OCPs
- GnRH agonists
- LNG-IUCD (Mirena)

Surgery for DUB

- These are uterus conserving **endometrial ablation** surgeries.
- **Indications**
 - Failed medical treatment in women who do not want menstruating or reproductive function
 - Women wanting to preserve uterus and avoid longer surgery.
- **Pre-requisites**
 - Woman's family should be complete
 - There should be no evidence of malignancy
- **Methods of endometrial ablation** are:
 - Laser (Nd:YAG) endometrial ablation
 - Transcervical resection of endometrium
 - Cryoablation
 - Uterine thermal balloon
 - Microwave balloon.

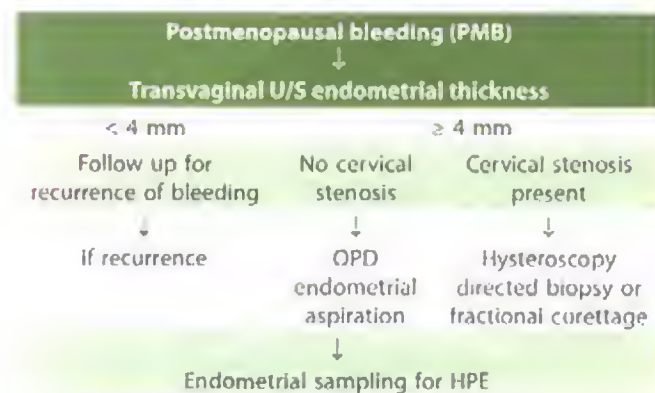
POSTMENOPAUSAL BLEEDING (PMB)

Definition: Any bleeding which occurs in a middle aged female **after 12 months of amenorrhea**.

MC cause of PMB in developed countries	Endometrial and vaginal atrophy
MC cause of PMB in developing countries (like India)	Ca cervix
MC Cancer causing PMB in India	Ca cervix
MC Cancer causing PMB	Ca endometrium
% of PMB patients who have endometrial cancer	15%

- Other causes of PMB: HRT, endometrial polyps, mendumetrial hyperplasia, endometrial cancer, cervical cancer.
- **First investigation** to be done when a patient comes with PMB is **Transvaginal ultrasound (TVUS)**.
- Further course of action following TVUS is given in following table.

Investigation of Postmenopausal Bleeding (PMB)



POLYCYSTIC OVARIAN DISEASE (PCOD)

- Aka *Stein-Leventhal* syndrome.
- ↑ **LH** production leads to **anovulation** and **hyperandrogenism** (due to deranged steroid synthesis).
- Enlarged bilateral **cystic ovaries** manifest clinically with **amenorrhea**, **infertility**, **obesity** and **hirsutism**.
- PCOD is also a/w **insulin resistance**. ↑ risk of **endometrial cancer**.
- Multiple small (1 cm) cysts lining periphery of both ovaries gives '**string of pearls**' appearance on USG.
- Tests:
 - Hormonal changes are given in following table.
 - **Positive progestin challenge** (administration of progestin causes uterine bleeding within 5 days of administration).

Increased hormones	Hormones decreased
<ul style="list-style-type: none"> • ↑ LH > 10 IU/mL, so that, LH : FSH ratio > 3 (i.e. increased LH:FSH ratio OR decreased FSH:LH ratio) • ↑ Androgens (↑ testosterone; ↑ DHEA, androstenedione) • ↑ Insulin 	<ul style="list-style-type: none"> • ↓ FSH • ↓ SHBG (sex hormone binding globulin) • Progesterone

- **Treatment:**
 - Medical treatment is mentioned in following table.
 - Surgery (**laparoscopic ovarian drilling**, endoscopic ovarian cauterization, CO₂ laser vaporization of cysts).

Symptom	Treatment
Obesity	Weight loss
For amenorrhea	OCPs

Contd...

Symptom	Treatment
For infertility (for inducing ovulation)	SERMs (Selective Estrogen Receptor Modulators): Clomiphene Metformin Gonadotropin analogs
For insulin resistance	Weight Loss Metformin (can be used in pregnancy also)
For hirsutism	OCPs + cyproterone acetate (See full details under next topic on Hirsutism)

EXTRA EDGE

- **Rotterdam:** Criteria is used for diagnosis of PCOD (2 out of 3 must be present for diagnosis of PCOD).
 - Ovulatory dysfunction (oligomenorrhea or amenorrhea)
 - Clinical (hirsutism/acne/alopecia) or biochemical evidence of hyperandrogenism (serum testosterone between 70 and 150 ng/dL).
 - Transvaginal USG - **12 or more cysts** (2-9 mm in diameter) in any one or both ovaries with increased **ovarian volume** > 10 mL (10 mm³).

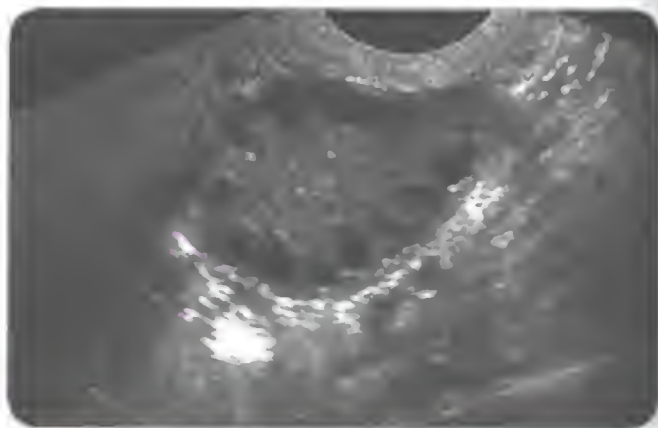
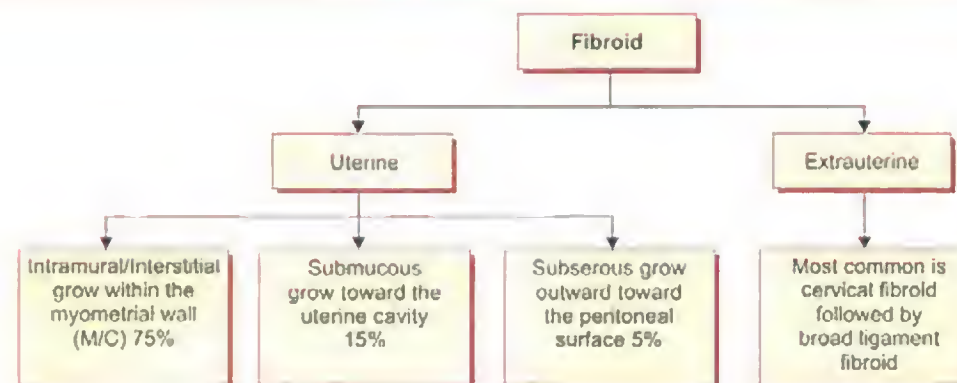


Fig. 25.10: USG photo of PCOS

HIRSUTISM

- Hirsutism is defined as **androgen-dependent** excessive male-pattern hair growth in females; It affects approximately 10% of women.
- **MC** cause is **idiopathic** > **PCOD**.
- Other causes are
 - Ovary related: PCOD; masculinizing tumors of ovary.
 - Adrenal related: Congenital adrenal hyperplasia; adrenal tumor; Cushing syndrome
 - **Drugs:** Minoxidil; phenytoin; diazoxide; cyclosporine; androgens; OCPs containing androgens.
- **Treatment**
 - First line treatment is **low dose OCPs** for 6 months at least.



- If no response, add **anti-androgen** (spironolactone).
- Next drug is **GnRH agonists** (Leuprolide, Goserelin, Nafarelin).

EXTRA EDGE

- Modified **Ferriman Gallwey** score is used for grading **hirsutism**. Maximum score is **36 (total 9 sites)**. If score > 8 (mild hirsutism); If score > 15 (moderate/severe hirsutism).

ENDOMETRIOSIS

- Presence of functioning endometrium in sites other than uterine mucosa is called endometriosis.
- **Sites:**
 - **Endometriosis** has been reported in **virtually every portion of the body** with the **EXCEPTION of the spleen**, which seems to **suppress endometriosis**
 - Ectopic endometrial tissue occurs **MC on ovaries** ('chocolate cysts').
 - other common sites include pelvic peritoneum, pouch of Douglas, Uterosacral ligaments, Rectovaginal epithelium, Sigmoid colon, Appendix, Pelvic lymph nodes and Fallopian tubes.
- **Theories of pathogenesis:**
 - Due to retrograde menstrual flow (Sampson's theory)
 - Coelomic metaplasia (Meyer and Ivanoff)
 - Lymphatic theory (Halban)
 - Direct implantation theory
 - Vascular theory
- **Symptoms:**
 - **Dysmenorrhea** (MC symptom).
 - **Pelvic pain**,
 - **Dyspareunia**
 - **Infertility**.

Diagnosis of endometriosis

- **Double puncture laparoscopic visualization** (gold standard).
- '**Powder burn**' appearance or '**matchstick spots**' on HSG is seen in pelvic endometriosis due to repeated hemorrhage and fibrosis into the affected areas.
- MCP-1 (Monocyte Chemoattractant Protein-1) is increased in peritoneal fluid of endometriosis patients.
- Serum CA-125 is also raised

Complications of Endometriosis

- Rupture of Infection of chocolate cyst
- Obstructive features: Intestinal obstruction; Ureteral obstruction (hydronephrosis)
- Malignancy is rare, MC being adenoacanthoma
- Endocrinopathy:
 - **Anovulation** (15%-25%)
 - **Hyperprolactinemia**
 - Luteolysis due to increased PGF2 alpha
 - Abnormal follicular genesis
 - Premature follicular rupture
 - **Luteinized unruptured follicles**
 - Luteal phase defect.

Treatment of Endometriosis

Expectant Treatment

Cases preferred are:

- Minimal endometriosis with no other abnormal pelvic finding
- Unmarried
- Young woman who is ready to start a family (pregnancy cures this condition)
- Approaching menopause

Hormonal Treatment

- Combined Oral Contraceptive Pill
- Progestogens (medroxyprogesterone acetate; norethisterone; dydrogesterone)
- IUCD, LNG-IUS (Levonorgestrel releasing IUCD)
- Danazol
- Gestrinone
- GnRH analogs (leuprolide, nafarelin, goserelin)

New Drugs in Treating Endometriosis

- Progesterone antagonists: **Mifepristone**
- Selective Progesterone Receptor Modulators (**SPRMs**): **Asoprisnil**
- **Dienogest** (synthetic progesterone)
- GnRH antagonist (**Cetrorelix**)
- **Aromatase inhibitors** (Anastrozole)
- **Simvastatin** (inhibits cell proliferation) and **Rosiglitazone** (reduces pain)

Surgery

- **Definitive Surgery:**
 - **Hysterectomy** with **B/L salpingo-oophorectomy**; resection of bowel or ureter maybe needed.
- **Conservative Surgery:**
 - Laparoscopic method: Cauterization; Laser vaporization; Laparoscopic uterosacral nerve ablation (LUNA); Adhesiolysis
 - Excision of rectovaginal nodules.
 - Laparoscopic ovarian cystectomy.

EXTRA EDGE

- **MC** site of **extrapelvic** endometriosis: GIT (MC Sigmoid colon > rectum)
- **MC** site for **urinary tract** endometriosis: Bladder > lower ureter
- **Allen Master's** syndrome: Endometriosis + pelvic peritoneal defects

ADENOMYOSIS

- Extension of **endometrium into the myometrium**.
- It is due to **dysfunction of the junctional zone** (transitional zone).
- On **MRI**, **JZ thickness** ≥ 12 mm suggests endometriosis (normally 5 mm).
- Patients are usually **parous** with **age > 40 years**.
- Present with **dysmenorrhea**, **menorrhagia**, **infertility**.
- On per vaginal exam: **Boggy enlarged** uterus is seen (size not more than 12–14 weeks pregnancy); mobility NOT restricted; NO associated adnexal pathology.
- **Halban's sign**: tender softened uterus on premenstrual bimanual examination.

- **Inv. of choice** is **MRI**; **First inv. done** is transvaginal ultrasound
- **Treatment:**
 - Hormonal treatment and OCPs are **NOT** effective
 - LNG-IUS (IUCD) is useful in young patients.
 - Treatment of choice: **Hysterectomy** (esp since most patients are parous and elderly).

FIBROID (UTERINE LEIOMYOMA)

- **MC benign tumor** of the uterus; it is **estrogen dependent** tumor.
- Tumor size may **increase with pregnancy** and **decrease with menopause**.
- **Chromosomal** abnormalities are detected in 40% of cases - **MC** chromosomal 12–14 long arm translocation and deletion of chromosome 7 maybe present.

Risk Factors for Fibroid

Increased risk	Decreased risk
Nulliparity	Multiparity
Blacks	Menopause
Alcohol consumption	Combined OCPs
High fat diet, Obesity	Smoking
Family history	Exercise
Hyperestrogenic state	
PCOD	

Secondary Degenerations in Fibroid

- **Hyaline** degeneration: **MC degeneration**, occurs commonly in the **central part** of tumor which is least vascular.
- **Cystic** degeneration: MC occurs **postmenopausally** and MC in **interstitial (intramural)** fibroid.
- **Fatty** degeneration
- **Calcific** degeneration: MC in **subserous** fibroids; when whole tumor is calcified it is called '**wombstone**'. (**NOTE**: Calcifications begin from periphery of fibroid and degenerations from the center).
- **Red** degeneration: see detailed following subtopic.
- **Sarcomatous** change: see detailed following subtopic.

Red Degeneration

- Seen MC in **second trimester (second half) of pregnancy** BUT can occur at other times of pregnancy and also in nonpregnant females.
- An **aseptic condition** where suddenly the fibroid becomes **acutely painful**, **enlarged** and **tender**.
- Patient presents with **acute abdominal pain**, vomiting, malaise and fever. **Raised ESR** and **leukocytosis** maybe seen.

- Pathology: Fibroid becomes **soft, necrotic** and is stained **salmon pink** or **red** (due to **thrombosed** vessels); **aseptic infarction** occurs; secondary infection may cause **fishy odor**.
- Diagnosis is by **ultrasound**.
- Treatment
 - **Conservative** management with analgesics and antipyretics; symptoms subside in 3–10 days.
 - **NO** antibiotics given; **NO** myomectomy done; **NO** termination of pregnancy done.

Sarcomatous Change

- Very **rare**; seen only in **<0.2–0.5%** of cases.
- If it occurs it MC leads to **leiomyosarcoma**.
- Malignancy is **MC in submucous** > intramural fibroid.
- Clinically suspected when a fibroid in a postmenopausal woman becomes **painful, tender, starts growing rapidly** and produces **systemic upset** and **pyrexia**.

Clinical Features

- Peak occurrence in women **20–40 years** of age.
- MC **asymptomatic**
- Other **MC presenting symptom** is abnormal uterine bleeding: **Menorrhagia**.
- **Infertility** (fibroid responsible for <3% cases of infertility); MC fibroid to cause infertility and abortion is **submucous fibroid**.
- Obstructed labor; PPH; urinary retention, constipation.
- Inv of choice is ultrasound.

Treatment

- Asymptomatic fibroids can be observed.
- **GnRH agonists** temporarily to reduce size of tumor.
- **Myomectomy** was introduced by victor Bonney
- **Myomectomy** for resection of symptomatic fibroids in women wishing to maintain fertility. It should be performed in **immediate postmenstrual phase** to reduce blood loss during surgery. It should **NOT** be performed during pregnancy or cesarean section.
- **Hysterectomy** in women with **completed families** and in **associated malignancy**.

EXTRA EDGE

- **Bonney's** myomectomy clamp is used to reduce uterine artery blood flow during myomectomy; it is placed around the uterine vessels and round ligament.
- **MRG-HIFU**: Magnetic Resonance Guided High Frequency Ultrasound is also used in managing fibroid.
- **Wanstaker's classification** is a **hysteroscopic** classification of **submucous** fibroids.

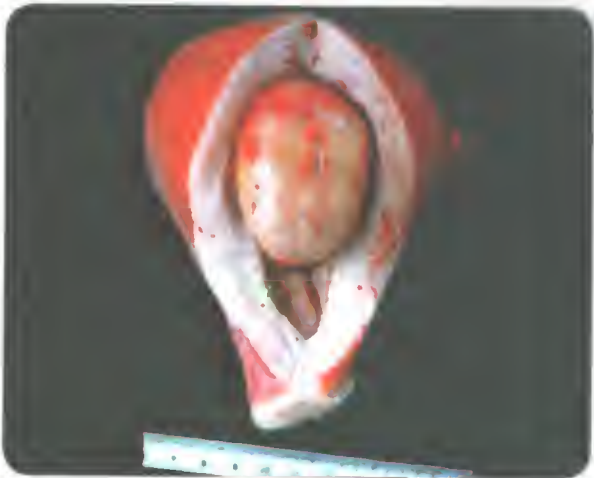


Fig. 25.11: Specimen of uterus with an intracavitary fibroid



Fig. 25.12: Myoma screw

INFERTILITY

- **Infertility** is the failure to conceive (regardless of cause) after **1 year** of unprotected intercourse.
- **Fecundability** is defined as the probability of achieving a pregnancy within one menstrual cycle. In a healthy young couple it is 25%.
- **Fecundicity** is the probability of achieving a livebirth within a single cycle.
- Infertility is caused by male and/or female factors.

Basic Investigations for Infertile Couple

- Semen analysis (**1st** investigation)
- Confirmation of ovulation
- Baseline U/S scan
- Assessment of tubal patency

Causes of Male Infertility

Pretesticular causes	Testicular Causes	Post-testicular causes
<ul style="list-style-type: none">Endocrine (congenital/ acquired diseases of the hypothalamus, pituitary, or peripheral organs that alter the hypothalamic-pituitary axis.Ex: idiopathic hypogonadotropic hypogonadism, prolactinoma, gonadotropin deficiencies, hyperprolactinemia and Cushing syndrome.Drugs (antihypertensives, antipsychotics)Psychosexual (impotence, erectile dysfunction)Genetic (47XXY- Klinefelter's) and Y chromosome deletions	<ul style="list-style-type: none">Genetic: Klinefelter syndrome is the MC chromosomal cause of male infertility and results in primary testicular failure.Nongenetic: Drugs, radiation, infections, trauma, and varicoceles	<ul style="list-style-type: none">Factors that do not allow the normal transport of sperm through the ductal system.Congenital:<ul style="list-style-type: none">Men who were exposed to DES in utero may have ductal obstruction.Congenital bilateral absence of the vas deferens (CBAVD)Young's syndrome (epididymal obstruction + bronchiectasis)Acquired: Infections, surgical procedures, and trauma may cause ductal blockage

CBAVD

- Congenital bilateral absence of the vas deferens (**CBAVD**) is responsible for 1–2% cases of male infertility.
- It is a/w **CFTR gene** mutation (80% cases) and cystic fibrosis.
- Also a/w seminal vesicle agenesis, low semen volume, low pH (acidic semen) with low fructose and azoospermia.
- CFTR mutation negative CBAVD is a/w renal anomalies (horseshoe kidney, aplasia, renal ectopy).

Markers of Function

Structure	Marker
Prostatic function	Acid phosphatase, zinc, citric acid
Seminal vesicle function	Fructose, prostaglandins
Epididymal function	Free L carnitine; Glycerophosphocholine, neutral alpha glucosidase

Semen Analysis

- First investigation** to be done when a couple presents with infertility.
- Abstinence of **3 days** is required.
- Collected by **masturbation** and transport to lab within 1 hour; keep as close to body temperature as possible.

Semen Analysis Parameters (WHO 2010)

Semen analysis	Normal value (basic minimum)
Volume	≥ 1.5 mL
pH	7.2–7.8
Viscosity	< 3 (scale 0–4)
Sperm concentration	≥ 15 million/mL

Contd...

Semen analysis	Normal value (basic minimum)
Total sperm count	39 million/ejaculate
Motility	Progressive motility = 32%
Morphology	Normal forms > 4%
Viability	Living 58%
Leucocytes	< 1 million/mL
Round cells	< 5 million/mL
Sperm agglutination	< 10% spermatozoa with adherent particles

- Semen should clot soon after ejaculation due to enzyme in the seminal vesicle but **liquefy in 30 minutes** due to prostatic enzyme. Semen is normally *viscous* and contains **fructose**.
- Normal male fertility** requires a count of > **15 million/mL** and a progressive motility of > **32%**.
- Most important** criteria in sperm analysis is **sperm morphology** > sperm motility > sperm concentration.

‘Spermia Nomenclature’

Term	Explanation
Azoospermia	Absence of sperm in the semen
Hypospermia	Low semen volume < 2 mL per ejaculation
Hyperspermia	Increased semen volume > 8 mL per ejaculation
Oligozoospermia	Sperm count of < 15 million sperm/mL
Polyzoospermia	Sperm count of > 350 million/mL
Asthenozoospermia	Reduced sperm motility of < 50%
Necrozoospermia	Spermatozoa are dead or motionless

Contd...

Contd

Term	Explanation
Teratospermia	↑↑ Abnormal sperm morphology at the head, neck, or tail level
Aspermia	No ejaculate (ejaculation failure)
OligoAsthenoteratozoospermia (OAT)	All sperm variables abnormal
Leucocytospermia	Increased WBCs in semen
Necrozoospermia	All sperms non-viable or non-motile

The Postcoital Test (Sims-Huhner test)

- Evaluation of the amount of spermatozoa and its motility within the cervical mucus during the preovulatory period.
- Done in **late proliferative** phase **8–12 hours after** coitus.
- Presence of active motile sperm numbering at least **10 per HPF** is satisfactory.
- NOT routinely performed since limited diagnostic potential and poor predictive value.

Management Options in Male Infertility

- Intracytoplasmic Sperm Injection - ICSI, (described here)
- In Vitro* Fertilization - IVF (described later)
- Intra Uterine Insemination (IUI)

Intracytoplasmic Sperm Injection (ICSI)

- Indications**
 - It is the **treatment of choice** where the male partner has azoospermia or severe oligospermia.
 - Also indicated for men with significant **antisperm antibodies**, **low sperm motility**, or significantly **abnormal sperm morphology** (Kruger strict morphology <4%).
 - Also used in IVF failure.
- Drawbacks**
 - The potential **transmission of a genetic abnormality** is a possibility when ICSI is performed. The normal barrier for morphologically abnormal sperm that tend to have genetic abnormalities (i.e. **zona pellucida**) is bypassed with ICSI.
- Procedure**
 - A single sperm is directly injected into a **mature metaphase II** egg. After this intrauterine transfer of the fertilized eggs is done.

Intra Uterine Insemination (IUI)

- IUI is the placement of **0.3–0.5 mL** of washed, processed and concentrated sperms (devoid of seminal plasma)/semen **into the uterine cavity by transcervical catheterization**.

- The patient lies **supine for 15 minutes** after sperm delivery.
- Thus the **cervical canal is bypassed** and increased number of motile sperms can be placed near the Fallopian tube for a higher chance of fertilization to take place naturally.
- Best results are achieved when the final specimen contains **10 million** total motile sperms.
- Timing of IUI
 - In natural and clomiphene stimulated cycles, urinary LH is monitored and IUI is done **on the day after mid cycle urinary LH surge** OR IUI is done 5–7 days after completion of clomiphene.
 - If ovulation is triggered by **exogenous hCG**, IUI is done **36 hours** later.
- Indications are given in table.

IUI is done in males with	IUI is done in females with
<ul style="list-style-type: none">Severe hypospadiasNeurogenic impotenceLow ejaculate volumeRetrograde ejaculation (immediate postcoital urine is taken and sperms are extracted from it)	<ul style="list-style-type: none">Cervical infertility: Antisperm antibodies in cervixVaginismus

Causes of Female Infertility

Cause	Comments
Ovarian causes	Ovulatory failure - Anovulation is MC cause (30–40%); Also the most easily reversible and treatable cause
Tubal causes	Infection/inflammation (PID, endometriosis) (30%)
Cervical causes	Stenosis or abnormalities of the mucus-sperm interaction
Uterine causes	Congenital defects: uterine/Mullerian anomalies Acquired: endometritis, fibroids
Others	Advancing age, Peritoneal (PID, adhesions, and adnexal masses)

Diagnosis of Ovulation

By Menstrual History

- Ovulation is usually inferred when a woman reports regular cycles between ages of 20 and 35.
- Midmenstrual bleeding (spotting) or pain on excessive mucoid vaginal discharge (**Mittelschmerz**)
- Features of premenstrual syndrome or primary dysmenorrhea.

Basal Body Temperature

- Body temperature maintained during first half of the cycle is **raised** by 0.5–1.0 °F (0.2–0.5 °C) **following ovulation**. The rise sustains during the second half of the cycle and falls about 2 days prior to the next period - '**biphasic pattern**' of temperature variation in ovulatory cycle.
- Oral temperature is taken daily morning on waking up before rising out of bed.

Cervical Mucus Study

- **Disappearance of the ferning** pattern of cervical mucus beyond 22nd day of cycle suggests ovulation.
- Following ovulation there is loss of **stretchability** (*spinnbarkeit*) which was present in midcycle.

Hormone Estimation

- **Serum Progesterone** estimation is done on day 8 and day 21 of a menstrual cycle (28 days). Increase in value from < 1 ng/mL to > 6 ng/mL is indicative of ovulation.
- **Serum LH** — Ovulation occurs about 34–36 hours after **LH surge**.
- **Serum estradiol** attains the peak rise approximately 24 hours prior to LH surge and about 24–36 hours prior to ovulation.
- The serum LH and estradiol is used for IVF.
- **Urinary LH**: Ovulation occurs within 14–26 hours of detection of urine LH surge and almost always within 48 hours.

Endometrial Biopsy

- Done on **21st–23rd day** of the cycle.
- **Subnuclear vacuolation** of the endometrial glandular epithelium is the **earliest evidence** of ovulation (36–48 hours).

Transvaginal Ultrasonography (TVS)

- Serial TVS during midcycle can precisely measure the **Graafian follicle** just prior to ovulation (**19–20 mm**).
- It is very helpful for confirmation of ovulation following ovulation induction, artificial insemination and IVF.
- Features of recent ovulation are **collapse of follicle** and **fluid in the pouch of Douglas**.

Laparoscopy

- Laparoscopic **visualization of the recent corpus luteum** or detection of ovum from the aspirated peritoneal fluid from pouch of Douglas is the **only direct evidence of ovulation**.

Pregnancy

- Pregnancy is the **100% surest evidence** of ovulation.

Tests to Assess Tubal Patency**Dilatation and CO₂ insufflation test (Rubin)**

- **Obsolete** test, NOT done now.

- Was done in the **postmenstrual phase, 2 days after** stoppage of menstruation.

Hysterosalpingography

- **Investigation of choice** and **first test** to assess tubal patency - since it is an OPD procedure, NO anesthesia required.
- Done in the **early follicular phase; Day 10 of the cycle** to minimize chances of interrupting a pregnancy.
- Radio-opaque dye is inserted with **Leech Wilkinson cannula** and fluoroscopic X-rays are taken.
- **MC** cause of B/L cornual block of HSG is **physiological** (due to cornual spasm); thus HSG cannot differentiate between cornual block and cornual spasm (**hence it is not the gold standard test**).



Fig. 25.13: Rubin/Leach Wilkinson cannula

Saline infusion sonography

- SIS should be performed **during cycle days 6–12** so that the endometrium is thin, allowing better detection of intrauterine lesions. In addition, this ensures that an undiagnosed pregnancy is not disrupted.
- **Transvaginal U/S** is done after instillation of sterile water/saline into the uterine cavity.
- While the SIS can confirm tubal patency, it does NOT provide information about the contour of the tubes. Thus, if a patient has a history of endometriosis or other tubal disease, an HSG would be preferred.

Laparoscopy and chromopertubation/Fallopscopy

- **Gold standard** test since it assesses BOTH tubal patency and visualizes the exterior of the tube.
- It is BOTH **diagnostic and therapeutic** as any pathology can be corrected by operative laparoscopy.
- BUT General Anesthesia is required and hence NOT the first test performed for tubal patency.
- **Chromopertubation** is where a dye (indigo carmine) is instilled through the Fallopian tubes during laparoscopy to visually document patency.

Test to Assess Ovarian Reserve

- Ovarian reserve tests are done to *assess how well the woman will respond to ovulation induction therapy*, i.e. it assesses the **reproductive potential** of the woman. These tests assess the quantity as well as quality of primordial follicles in the woman's ovary.
- Tests done are
 - Serum day 3 FSH levels
 - Serum inhibin B levels
 - Clomiphene citrate challenge test
 - Serum anti-Müllerian Hormone test: **Best test**
 - Antral Follicle Count (AFC) test: **quantitative marker** of ovarian reserve.

Treatment of Female Factor Infertility

- **Cervical, Tubal** and **Uterine** structural anomalies may need **surgical correction** and medical treatment (endometriosis) wherever necessary.
- Ovulatory factors need **Ovulation induction**: the appropriate treatment for infertile patients who have dysfunction of the hypothalamic-pituitary-ovarian axis.
- The ovulation induction agents are
 - Clomiphene citrate
 - hMG (human menopausal gonadotropin)
 - hCG
 - GnRH analogs and
 - Bromocriptine

Clomiphene Citrate

- CC blocks estrogen receptors → increase FSH from pituitary (due to loss of negative feedback of FSH) → growth of multiple follicles → multiple gestation.
- It can be used only in patients with **intact hypothalamo-pituitary-ovarian (HPO) axis**.
- **50 mg/day for 5 days** is given from D2–D6 or D5–D9. From D10 follicular monitoring is done and as follicle reaches 18–20 mm size; **hCG** is given to **trigger ovulation**.
- Suitable patients for clomiphene citrate (CC) are
 - Normogonadotropic, normoprolactinemic
 - PCOS with amenorrhea or
 - Hypothalamic amenorrhea
- For women with PCOS who do not ovulate with CC, insulin sensitizers (**metformin**) and/or **laparoscopic ovarian drilling (LOD)** is effective in inducing ovulation.
- For women with **hyperprolactinemia**; **bromocriptine** can be used along with CC.
- Side effects

- Risk of **multiple gestation** is about 5% (mostly twins).
- Hot flashes (**MC** side effect)
- Incidence of miscarriage, ectopic or congenital malformations is **NOT** increased.
- Risk of ovarian hyperstimulation syndrome (**OHSS**) is < 1%.
- Side effect due to which it should be stopped immediately is **visual symptoms**.

HMG

- Human menopausal gonadotropin (HMG) is extracted from the urine of postmenopausal women.
- Maximum dose is **450 IU**.
- Risk of multiple pregnancy is **30%** and risk of OHSS is **15%**.

Ovarian hyperstimulation syndrome

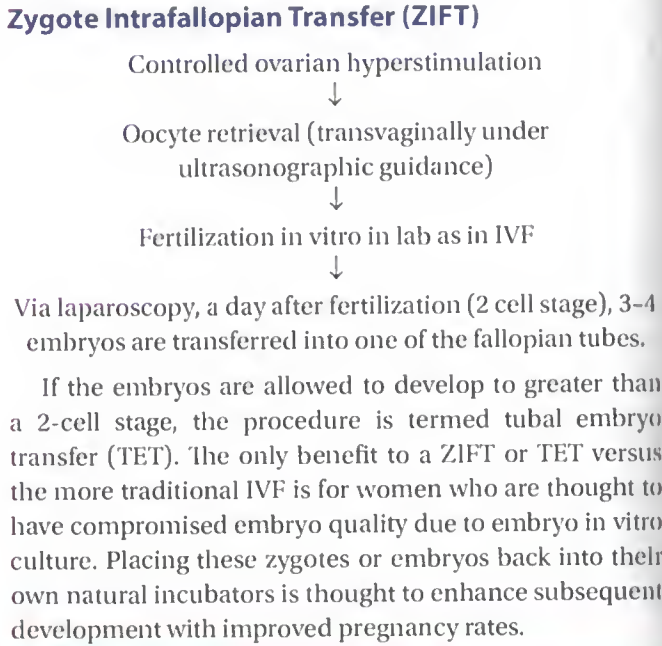
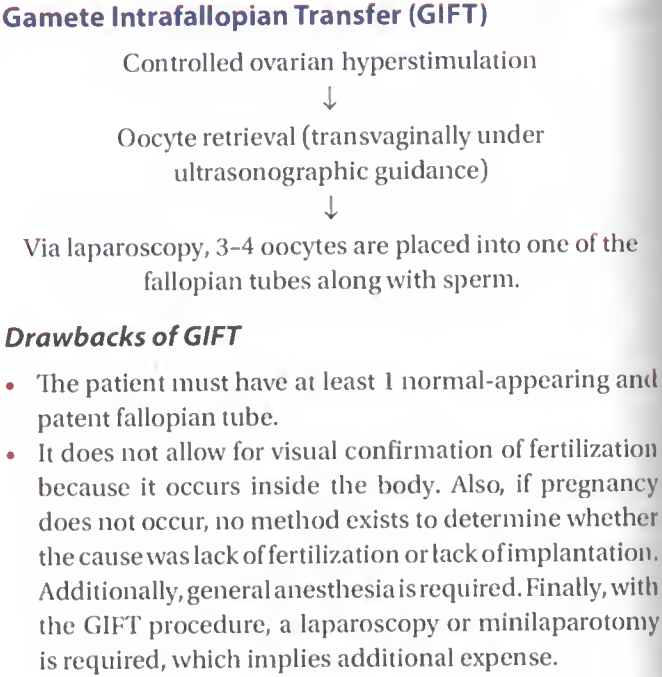
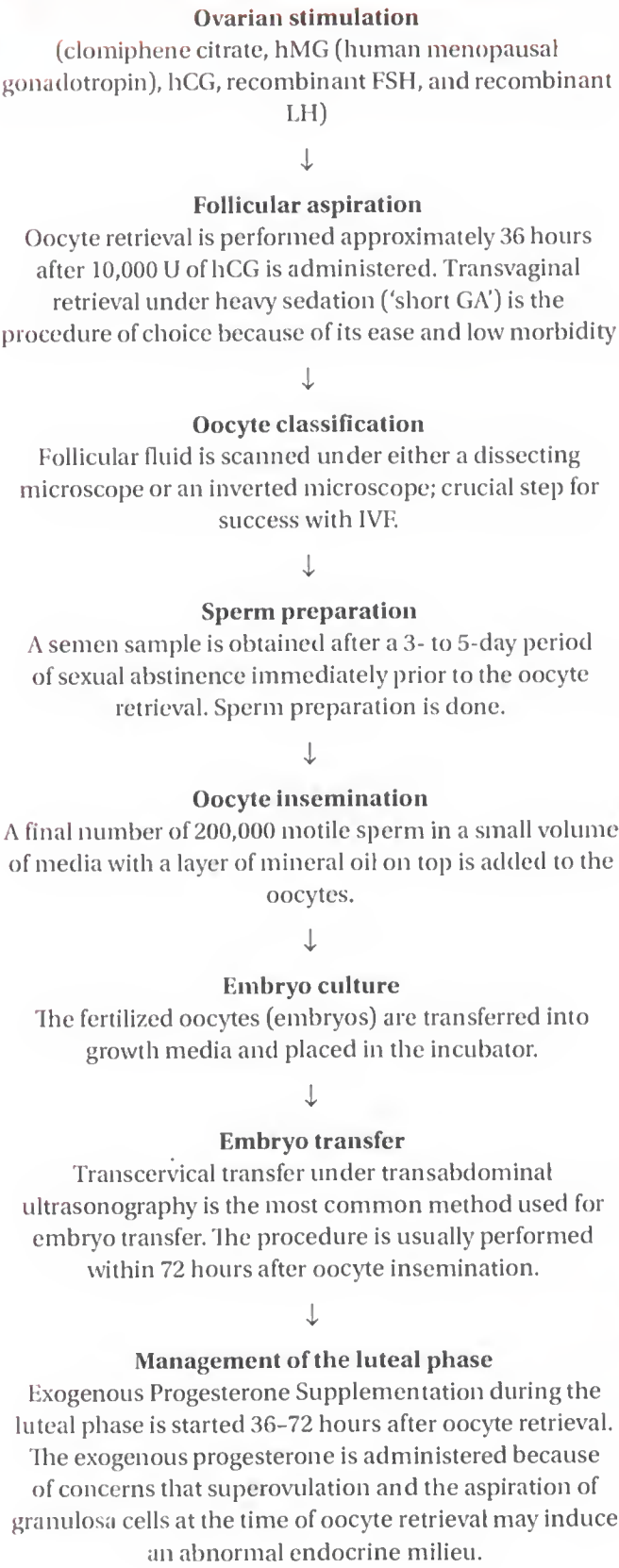
- **Ovarian hyperstimulation syndrome (OHSS)** is a complication of ovulation induction
- Basic pathology is **increased capillary permeability (VEGF)** leading to ascites, hypovolemia, oliguria and electrolyte imbalance
- Management is medical
- Abdominal paracentesis to relieve respiratory distress and human albumin (IV) to correct hypovolemia maybe needed

IN VITRO FERTILIZATION (IVF, 'TEST TUBE BABY')**Indications**

- Absence of the fallopian tubes and severe pelvic adhesions.
- Patients with a history of endometriosis unsuccessfully treated medically or surgically.
- Uterine malformation related to DES exposure during pregnancy.
- Patients with husbands who have severe oligospermia or a history of obstructive azoospermia.
- Patients who have failed more conservative therapies or with an unknown etiology of infertility.

Procedure

IVF consists of retrieving preovulatory oocytes from the ovary and fertilizing them with sperm in the laboratory, with subsequent embryo transfer (replacement) within the endometrial cavity. The following steps are required during an IVF cycle:



ENDOMETRIAL HYPERPLASIA

- Endometrial hyperplasia is important because
 - It causes *abnormal bleeding* and
 - It either precedes or occur simultaneously with *endometrial carcinoma*
- It is a/w **PCOD** and **glucose intolerance**.
- It maybe **simple or complex** hyperplasia - these can be further divided into 4 categories as shown in table.

Type of hyperplasia	Progression to cancer
Simple (cystic) hyperplasia without atypia (cystic glandular hyperplasia)	1% (Least)
Complex (adenomatous) hyperplasia without atypia	3%
Simple (cystic) hyperplasia with atypia	8%
Complex (adenomatous) hyperplasia with atypia	29% (Maximum)

- Treatment:
 - **Non-atypical** hyperplasia: Since chances of malignancy are less, they are managed medically with **progesterone** therapy.
 - **Atypical** hyperplasia: Ideal treatment is **hysterectomy** since chances of malignancy is high.

ENDOMETRIAL CARCINOMA

- **MC gynecologic malignancy** in *developed* countries.
- Peak age is **55–65 years**.
- MC presents with **postmenopausal bleeding**.
- Transvaginal U/S, endometrial biopsy, CXR (to look for metastases).

Risk Factors

Category	Risk factor
Prolonged unopposed estrogen exposure	Atypical Endometrial hyperplasia Early menarche - late menopause Nulliparity Obesity (peripheral conversion to estrogen) Estrogen replacement therapy Tamoxifen (anti- and pro-estrogenic activity) Chronic anovulation Secondary infertility
Family history	Hereditary Non-Polyposis Colorectal Cancer (HNPCC, Lynch type 2) syndrome: aw higher incidence of endometrial, colonic, ovarian, urinary, biliary, gastric and small intestinal cancer
Associated medical conditions	Diabetes, HTN

EXTRA EDGE

- Protective factors for Ca endometrium
 - OCPs
 - Smoking
 - Multiparity
 - Physical exercise

Classification

- **Adenocarcinoma (endometroid) Ca - MC type, >80%.**
- Adenosquamous Ca
- Mucinous Adeno Ca
- Papillary serous Adeno Ca - **Highly malignant**
- Clear Cell Adeno Ca - **Highly malignant**, Affects **older age**; a/w **hobnail** cells
- Squamous Ca
- Secretory Adeno Ca
- Mixed and Undifferentiated Ca

Features	Type I (endometroid, 80%)	Type II (Non-endometroid, 20%)
Risk factor	Unopposed estrogen	Age
Menopausal status	Pre and perimenopausal	Postmenopausal
Endometrial hyperplasia	Present	Absent
Tissue differentiation	Well	Poor
Myometrial invasion	Minimal	Deep
Subtypes	Endometroid, Adenoca	Papillary serous, clear cell
Behavior	Stable	Aggressive
Ploidy	Polyploid	Aneuploid
Molecular characters	PTEN mutations	Her2/Neu expression; p53
Prognosis	Favorable	Not favorable

Investigation

- **First investigation** is TVS (**transVaginal ultraSound**) since the first investigation for postmenopausal bleeding is TVS (see Table under topic Postmenopausal bleeding in this chapter).
- Investigation of choice is **endometrial aspiration biopsy**.
- Gold standard investigation is **fractional curettage**.

Staging

- Staging for Ca endometrium is done surgically; surgical staging includes **total abdominal hysterectomy (TAH)** + **Bilateral salpigo-oophorectomy (BSO)**.
- In case of clear cell and papillary serous Ca, **omentectomy and peritoneal biopsy** is done.
- **Lymphadenectomy** is also done in clear cell Ca and in cases where > 50% myometrium is involved.

Stage	Description
Stage 1	Tumor confined to the uterine corpus
1a	Tumor confined to the endometrium
1b	Tumor invasion < 1/2 of the myometrial thickness
1c	Tumor invasion > 1/2 of myometrial thickness
Stage 2	Tumor reaches the cervix
	Involvement of cervical stroma ; ONLY cervical glandular involvement falls under Stage 1
Stage 3	Local spread beyond the uterus and cervix but not outside the true pelvis
3a	Serosal or adnexal invasion. Positive peritoneal cytology
3b	Vaginal metastases
3c	Metastases to pelvic (3C1) or para-aortic (3C2) lymph nodes
Stage 4	Distant spread or organ invasion
4a	Tumor invasion of bladder and/or bowel mucosa
4b	Distant metastases. Inguinal lymph node involvement

Treatment

- **Stage 1 and 2** — Extrafascial TAH + PSO. Stage 2 cases may also require adjuvant radiotherapy.
- **Stages 3 and 4** — TAH + BSO with postoperative radiotherapy.
- Some tumors respond well to progestogen therapy, particularly those with pulmonary and lymph node metastases. Brain and bone metastases respond best to external radiotherapy.
- **Recurrences:** *Vaginal vault* is the **MC site** of local recurrence following hysterectomy (10–15%).

EXTRA EDGE

- **‘Corpus cancer syndrome’** = syndrome of Obesity, Diabetes, Hypertension and Infertility – a/w uterine corpus (endometrial) cancer.

CERVICAL INTRA-EPITHELIAL NEOPLASIA (CIN)

- **Risk factors** for CIN are the same as those mentioned for Ca Cervix under the topic of Ca Cervix.
- **Bethesda classification** system is used to grade the dysplasia in CIN based on cytology smear of Pap test.
- Based on the *thickness of cervical epithelium which has become dysplastic*, CIN may be classified as shown here.

WHO	CIN	Description	Bethesda classification
Mild dysplasia	CIN I	Dysplastic cells seen in lower 1/3 of epithelium	LSIL (Low Squamous Intraepithelial Lesion)
Moderate dysplasia	CIN II	Dysplastic cells seen in lower 2/3 of epithelium	
Severe dysplasia	CIN III	Dysplastic cells seen in > lower 2/3 of epithelium	HSIL (High Squamous Intraepithelial lesion)
Ca in situ	Ca in situ	Dysplastic cells seen in full thickness of epithelium (but basement membrane is intact)	

- CIN is common in **20–30 years** age group.
- **MC site for CIN** is the **transformation zone (squamocolumnar junction, SCJ)**.
- SCJ is found in the *exocervix in neonates*; BUT it is a *dynamic part* and does not remain restricted to this area.
- It **moves inside** (not out) with age and hormonal influence.
- It **moves out** in pregnancy, at puberty and with OCP usage.

PAP Smear

- Started by Georgios **Papainkolaou**.
- PAP smear **screens for cervical dysplasia**, CIN and Ca in situ.
- PAP smear is started at **21 years** of age (irrespective of age of first intercourse).
- **Ayre’s spatula** and **endocervical brush** is used for the procedure.
- First sample is taken from *portio vaginalis of cervix* and second slide from *endocervix*.
- PAP smear is done approximately **2 weeks after first day** of last menstrual period.
- PAP smear has reduced incidence of cervical cancer by **80% and death by 70%**.
- Fixative used for PAP smear is **95% Ethyl alcohol**



Fig. 25.14: Ayre spatula

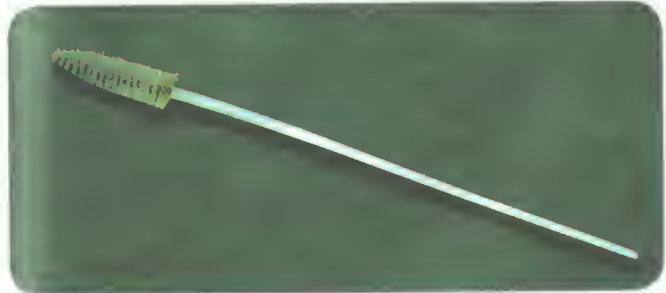


Fig. 25.15: Endocervical brush

Alternatives to PAP Smear (Cytology)

- **VIA** (Visual Inspection with Acetic acid): Speculum is introduced and cervix is stained with 5% acetic acid and inspected after 1 minute. Acetowhite lesions are considered for colposcopic examination and/or biopsy.
- **VILI** (Visual Inspection with Lugol’s Iodine, Schiller’s test): Speculum is introduced and cervix is stained with 3% Lugol’s iodine. Normal vaginal epithelial cells have glycogen and appear brown or mahogany in color; BUT dysplastic cells do not take up iodine and remain unstained, i.e. yellow in color.

Diagnostic Procedures for CIN

- **Colposcopy** is **gold standard** technique for evaluation of abnormal PAP smear (more below) when **lesion is NOT visible**.
- **Cone biopsy (conization)** is done to confirm findings of colposcopy, if there is a discrepancy between PAP smear result and colposcopy. The need for diagnostic cone biopsy has been **reduced by at least by 80%** due to use of *colposcopy directed biopsy*.
- **Punch biopsy** is done to confirm findings of abnormal PAP smear when **lesion is visible**.

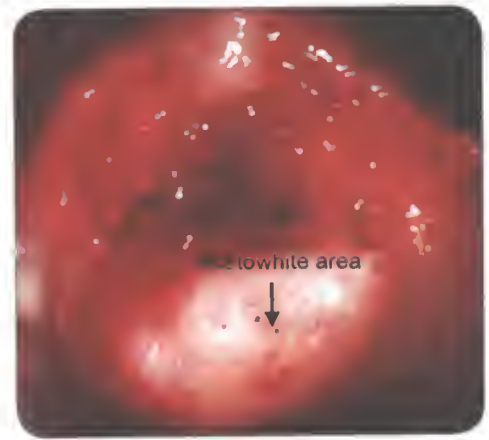
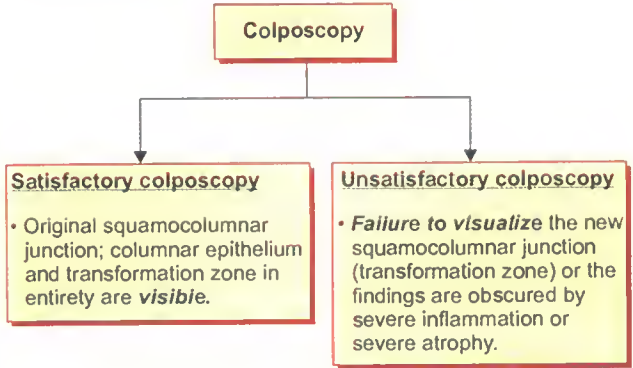


Fig. 25.16: Acetowhite area on colposcopy

Colposcopy

- **Colposcopy** is a procedure whereby using an instrument called colposcope, the **cervix** is visualized under high magnification (**10–20 times**) so that selective **biopsy** can be obtained from abnormal areas.
- In **colpomicroscopy**, the magnification is **100–300 times**.
- Important parameters of colposcopic examination are: *margin; color; vascular patterns and Lugol solution staining (Reid index)*.
- Abnormal colposcopic findings:
 - White epithelium - **leukoplakia**
 - **Acetowhite** epithelium—turning white following application of 5% acetic acid due to cell protein coagulation
 - Punctuation—dilated capillaries which appear on the surface as dots (end on view of vessels)
 - Mosaic—capillaries encircling polygonal shaped blocks of epithelial cells
 - Atypical blood vessels
 - Irregular surface contour.



Cone Biopsy (Conization)

- Cone biopsy involves removal of a cone of cervix which includes a part of ectocervix, entire SCJ and endocervix.
- It is **BOTH** diagnostic and therapeutic for CIN.
- It can lead to **incompetent os** and subsequent recurrent second trimester abortions.
- Done in **OT under GA**.
- It is usually done with conventional knife (**cold knife**). (Currently it is being done under colposcopic guidance with **CO₂ laser under LA**).
- Bleeding is the MC complication.
- Indications:
 - Unsatisfactory colposcopy: When limits of lesion or the SCJ cannot be visualized by colposcopy.
 - Positive endocervical curettage (in HSIL).
 - Ca in situ in young females.

Treatment of CIN

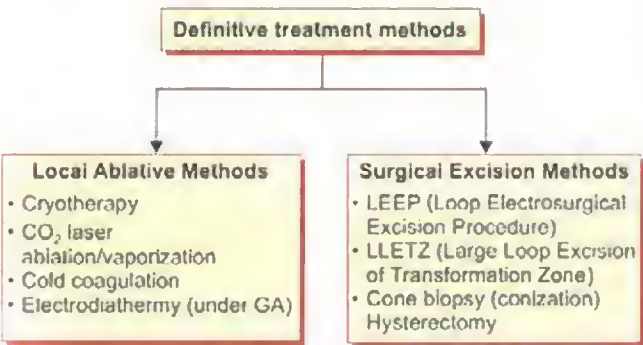
- Preventive treatment: HPV vaccines (see below)
- Definitive treatment: See flowchart

HPV Vaccines

- Developed from the *inactivated capsid coat* of the virus.
- Vaccines are effective for at least **7.5 years**.
- Immune defense is *type specific* and is effective only when given prophylactically.
- Ideal age for of vaccination girls is **9–13 years**.
- All vaccines are given as **0.5 mL IM**.
- **WHO** recommendation:
 - Girls < **15 years**: 2 dose at 0 and 6 months
 - Girls > **15 years**: 3 doses at 0, 1 and 6 months

Characteristic	Bivalent vaccine (2V HPV)	Quadrivalent vaccine (4V HPV)	Nonavalent vaccine (9V HPV)
Brand name	Cervarix	Gardasil	Gardasil-9
Protects against subtypes	HPV 16, 18	HPV 6, 11, 16, 18	HPV 6, 11, 16, 18, 31, 33, 45, 52, 58
Protects against	CIN, Ca cervix	CIN, Ca cervix, anogenital warts	CIN, Ca cervix, anogenital warts, vulvar and vaginal intra-epithelial neoplasia
Administered to	Only females	Both males and females	Both males and females

Definitive Treatment Methods



Important points of the above methods are:

- **Depth of penetration:**
 - With cold agglutination: 4 mm
 - With cryotherapy: 5 mm

- With CO₂ laser: 7 mm
- With electrodathermy: 8–10 mm
- Cryotherapy acts on principle of crystallizing intracellular water at *minus 90°C*. It uses either *nitrous oxide or CO₂*. **Double freeze thaw** technique is most effective.
- Cold agglutination needs **NO** anesthesia; **III** electrodathermy is done under GA.

Treatments of choice in CIN

- CIN I: Observe and do yearly HPV and PAP smear every year
- CIN persisting beyond 2 years: Cryotherapy
- CIN II and III: LEEP
- CIN extending into the vaginal fornices: CO₂ laser ablation
- Recurrent CIN III: Hysterectomy

CARCINOMA CERVIX

- **Second MC cancer** in females in India (and the world) after *Ca breast*.
- MC age group affected: **Bimodal** peak-1st peak at 35–39 years and 2nd peak at 60–65 years.

Risk Factors for CIN and Ca Cervix

- **HPV** infection - *most important* risk factor (see more below)
- Sexually transmitted infections, HIV, Chlamydia, HSV2
- Early intercourse (< 18 years)
- Multiple sex partners
- Multiparity
- Poor personal hygiene
- Poor socio-economic status
- Smoking (predisposes to squamous cell ca)
- OCPs (predisposes to Adeno Ca)
- Immunosuppression
- In utero exposure to DES (diethylstilbestrol)

Human Papilloma Virus

- **Most important** and **MC** risk factor for Ca cervix.
- **High** oncogenic risk HPV = **16, 18, 31, 33, 35, 45, 56**.
- **Low** oncogenic risk HPV = **6, 11, 42, 43**.
- **Over 99.7% patients** with CIN and invasive Ca cervix are found to be positive with high risk HPV.
- HPV DNA detection methods: PCR, Southern blot, Hybrid capture-2 (**HC-2**).
- HPV is **epitheliotropic**; HPV infected cells show **koilocytosis** characterized by enlarged cells with large, irregular hyperchromatic nuclei and perinuclear halos [*Koilocytes image has been given under viral warts in Dermatology chapter (Pg 1057)*].

Pathology

- MC Ca cervix occurs in the **ectocervix (80%)**
- Maybe *exophytic (from ectocervix)*; ulcerative or *infiltrative (from endocervix)*.

Squamous cell carcinoma	Adenocarcinoma (20%)
MC type of Ca cervix (80%)	Accounts for 20% of ca cervix
Arises from the squamo-columnar junction	Arises from endocervix
Subdivided into <ul style="list-style-type: none">• Large cell keratinizing (MC type)• Large cell nonkeratinizing• Small cell (worst prognosis)• <i>Verrucous Ca</i> - a/w HPV6, slow growing and locally invasive; resembles condyloma acuminata; needs radical resection	MC in <i>young females</i> A/w <i>Progestosterone OCP</i> pill usage MC subtype is <i>mucinous endocervical</i> Adeno Ca a/w HPV 18. Adenoma malignum is extremely well differentiated Adeno Ca with favorable prognosis

Clinical Features

- MC symptom is **bleeding per vaginum**.
- **Vaginal discharge** that is initially clear, but later becomes offensive.
- **Pelvic pain**, often unilateral.
- Four cardinal signs are: **hardness, friability, fixation and bleeds on touch**.

Mode of Spread

- **MC route** is **lymphatic** spread.
- Other routes are direct spread and hematogenous spread.
- MC hematogenous spread occurs in **lungs**.

Other Important Points

- **Downstaging of Ca cervix** (detection of disease at an early stage when it is still curable) is done by nurses and paramedical personnel by **simple speculum inspection** of the cervix.
- **MC lymph node** involved in Ca cervix is **obturator node**.
- **MC cause of death** in Ca cervix is **uremia (renal failure, MC)** > **hemorrhage** (Second MC); other causes are sepsis, cachexia and metastases to the lung.
- Biopsy of concerning lesions (punch or cone) is required to make a formal **histologic diagnosis**.

Staging of Ca Cervix

- Staging of Ca cervix is principally based on clinical examination.

- USG/CT/MRI/PET/laparoscopy/laparotomy and lymphangiography are **not included** in investigations for staging Ca cervix approved by FIGO.
- Staging procedures allowed by FIGO are mentioned in Table.

Clinical examination	Extent and depth of tumor spread detected by	Supplementary investigations
<ul style="list-style-type: none">• Lymph node palpation• Inspection of cervix and vagina• Pelvic examination under anesthesia- speculum exam, bimanual and rectal exam)	<ul style="list-style-type: none">• Colposcopy• Hysteroscopy• Cystoscopy• Biopsy• Endocervical curettage• Conization	<ul style="list-style-type: none">• Chest X-ray (for lung metastases)• Skeletal X-ray (for bonet metastases)• IVU/USG (for hydronephrosis)• Barium enema (for large bowel involvement)• Proctoscopy (for rectal involvement)

FIGO Staging of Ca Cervix (2009)

Stage	Invasive carcinoma
I	Ca confined to cervix ONLY strictly
IA	Diagnosed only by microscopy with deepest invasion < 5 mm and largest extension < 7 mm
IA1	Measured stromal invasion < 3 mm in depth and horizontal extension < 7 mm
IA2	Measured stromal invasion between 3 and 5 mm with horizontal extension < 7 mm
IB	Clinically visible lesion limited to cervix uteri or preclinical cancer greater than stage IA
IB1	Clinically visible lesion < 4 mm in greatest dimension
IB2	Clinically visible lesion > 4 mm in greatest dimension
II	Ca Cervix invades beyond the uterus but NOT to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion < 4 mm in greatest dimension
IIA2	Clinically visible lesion > 4 mm in greatest dimension
IIB	With obvious parametrial invasion
III	Tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
IIIA	Tumor involves lower third of the vagina with no extension to pelvic wall

Contd...

Stage	Invasive carcinoma
IIIB	Extension to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
IV	Tumor extends beyond true pelvis or has involved (biopsy proven) the mucosa of bladder or rectum
IVA	Spread of growth to adjacent organs
IVB	Spread to distant organs

Treatment of Ca Cervix

- All stages of Ca cervix are **radiosensitive**.
- Ca cervix was the **first cancer of an internal organ** to be treated using ionizing radiation by Margaret Cleaves in 1903.

Stage	Treatment of choice
IA1, IA2, IB and IIA	Surgery <ul style="list-style-type: none">▪ Stage IA1: Simple hysterectomy▪ Stage IA2: Modified Radical (Wertheim's) hysterectomy▪ Stage IB1: Radical hysterectomy
IIB-IVA	NOT operable and chemoradiation (radiotherapy + weekly cisplatin based chemotherapy) is the treatment of choice

Follicular cyst	Corpus luteum cyst	Theca-Lutein cyst
<ul style="list-style-type: none">▪ MC functional ovarian cyst.▪ Graafian follicle fails to rupture during ovulation.▪ Usually asymptomatic.▪ Size is 4-8 cm mass that is lined by granulosa cells.▪ Cyst < 3 cm - observation only.▪ Cyst < 7 cm with CA-125 normal should be followed up 6 monthly.	<ul style="list-style-type: none">▪ Occurs due to overactivity of corpus luteum which fails to regress BUT becomes cystic or hemorrhagic. More likely to rupture causing pain and hemoperitoneum.▪ Right sided cysts usually rupture especially during intercourse.▪ If causing acute abdomen - laparoscopy and cyst enucleating is required.	<ul style="list-style-type: none">▪ Usually bilateral and caused due to excessive hCG.▪ Seen in molar pregnancy, multiple gestation, choriocarcinoma, diabetes mellitus, ovulation induction (clomiphene or HMG or GnRH analog usage).▪ They can reach upto 30 cm and are generally multicystic and resolve spontaneously.

CLASSIFICATION OF OVARIAN TUMORS (WHO)

- **Epithelial tumor (MC, 60-70%)**
 - **Serous** cystadenoma, serous cystadenocarcinoma
 - **Mucinous** cystadenoma; mucinous cystadenocarcinoma
 - **Endometroid** tumors
 - **Mesonephroid** or **clear cell** tumors
 - **Brenner** (*Transitional cell*) tumor
 - **Squamous** cell tumor
 - Mixed epithelial tumor
 - Undifferentiated carcinoma
- **Sex cord stromal tumors (10%)**
 - **Granulosa** cell tumors (*estrogen secreting*)

EXTRA EDGE

- **Microinvasive** = Stage IA; **Early Invasive** = Stage IB, IIA; **Advanced** = Stage IIB-IV.
- **Radical trachelectomy** is an alternative to radical hysterectomy for young women wishing to preserve fertility. Suitable for **early stage (IA2 or small IB1) cancers**. This procedure involves removal of 80% of cervix, parametria and vaginal cuff along with pelvic lymphadenectomy.
- **LAVRT** = Laparoscopic Assisted Vaginal Radical Trachelectomy with pelvic and aortic lymphadenectomy.
- Cervical cancer is the **MC malignancy in pregnancy**.
- Ca cervix detected within first 6 months of treatment is called **persistent cancer**; If detected after 6 months, it is called **recurrent cancer**.

PHYSIOLOGIC/FUNCTIONAL CYSTS OF THE OVARY

- Ovarian cyst occurs due to fluid accumulation in the ovary.
- They are the **MC adnexal mass** in the reproductive age group.
- They are usually **asymptomatic** and **spontaneously resolve** in 4-6 weeks.

- Tumors of **thecoma-fibroma** group (*estrogen secreting*)
 - Thecoma
 - Fibroma
 - Unclassified
- **Androblastoma** (*Androgen secreting*)
 - **Sertoli** cell tumor
 - **Sertoli-Leydig** cell tumor
 - **Hilus** cell tumor
- Gynandroblastoma
- Unclassified
- **Lipid cell tumor**
- **Germ cell tumors (20%)**
 - **Dysgerminoma**

- **Endodermal sinus** tumor (**yolk sac** tumor)
- Embryonal cell carcinoma
- Polyembryoma
- Choriocarcinoma
- **Teratoma**: Immature, mature (dermoid cyst), monodermal (struma ovarii, carcinoid).
- **Gonadoblastoma**
- **Unclassified**
- **Gestational trophoblastic diseases**
- **Secondary metastasis**

BENIGN OVARIAN NEOPLASMS

- 75% of ovarian neoplasms are benign.
- Ovarian neoplasms (both benign and malignant) maybe derived from any of these 3 sources
 1. **Epithelium** (derived from coelomic epithelium)
 2. Oocytes (derived from primitive **germ cells**)
 3. Mesenchymal elements (derived from **gonadal stroma**)
- These benign ovarian tumors are also referred to as '**ovarian cysts**'.
- Some of the common benign ovarian neoplasms are discussed here.

Serous Cystadenoma

- Accounts for **40%** of all ovarian tumors; Bilateral in **40%**; Chance of malignancy is **40%**.
- Lined with **Fallopian tube like epithelium**.
- Contain **Psammoma bodies**.

Mucinous Cystadenoma

- **Largest** benign ovarian tumor
- Multilocular cyst lined by mucus-secreting epithelium.
- A/w **pseudomyxoma peritonei**.

Brenner Tumor

- Rare adenofibromas in which epithelial cells resemble transitional epithelium (**Walther nests**).

Fibromas

- Bundles of spindle-shaped **fibroblasts**.
- '**Meigs' syndrome**' = ovarian fibroma, ascites and hydrothorax/pleural effusion.

Endometroid Tumor

- Consists of epithelial cells **resembling endometrium**.
- **Endometroid Ca** may occur.

Clear Cell (Mesonephroid) Tumors

- These tumors contain cells with abundant glycogen called '**hobnail cells**'.

Mature Teratoma ('Dermoid Cyst')

- **MC benign ovarian** tumor.
- Contains elements of all 3 germ layers:
 - **Ectodermal (MC)**: skin, teeth, hair, nail
 - **Mesodermal**: bone, cartilage, muscle
 - **Endodermal**: thyroid, salivary gland, bronchus, intestine

Typical USG sign of dermoid cyst ovary

- **White ball** appearance (corresponding to hair and sebum filling the tumor)
- **Dash and dot** appearance (multiple thin, echogenic bands caused by the hair in the cyst cavity)
- **Tip of the iceberg** sign (an echogenic interface at the edge of mass that obscures deep structures)
- **Rokitansky protuberance** solid projection of hair and sebum from surface of the ovary

- **Torsion** is the **MC complication**
- Many contain thyroid tissue (**struma ovarii**)
- Chance of **malignancy is low (1%)**.

MALIGNANT OVARIAN NEOPLASMS

Risk factors for ovarian cancer

- **Theory of incessant ovulation** implies that as frequency of ovulation increases, risk of ovarian cancer increases.
 - Early menarche and late menopause
 - Nulliparity
 - Family h/o ovarian cancer
 - Personal/family h/o breast cancer
 - Multiple cycles of gonadotropins/clomiphene citrate for ovulation induction
 - Diabetes mellitus
 - Obesity
 - Asbestos industry workers
 - Smoking (only for mucinous tumors)
 - Use of talc on perineum (for serous tumors)
 - Dyskinetic gonads
 - H/O endometriosis (for endometroid and clear cell tumors)

EXTRA EDGE

- **Protective factors for Ovarian cancer**: OCPs (since they cause anovulation); multiparity; breastfeeding; pregnancy; anovulation; tubal ligation; hysterectomy.

More About Risk Factors

- The average woman has about a **1.6% (1 in 72) lifetime chance** of developing ovarian cancer (with no family h/o ovarian cancer); in those with one first degree relative affected it is **5%** and two first degree relatives affected it is **7%**.
- The average woman has about a **12% (1 in 8) lifetime chance** of developing **breast cancer**.
- **Hereditary Breast Ovarian Cancer syndrome (BOC)**: Seen in **90%** ovarian cancers. BRCA-1 and BRCA-2 gene mutations are observed in majority of such cases.
- Hereditary Non-Polyposis Colorectal Cancer (**HNPCC, Lynch type 2**) in which cancers of proximal colon, endometrium, breast and ovary may occur.
- **CA-125** is a general ovarian cancer marker; good for monitoring progression, NOT for screening.

Serous Cystadenocarcinoma

- **MC malignant** ovarian tumor. Also **MC malignant** epithelial cell tumor of ovary.
- Age affected = **60-70** years.
- Presents with *vague* symptoms resembling *irritable bowel syndrome*, hence **detected late** and presents with **pelvic mass**.
- **CA-125** is raised.

Mucinous Cystadenocarcinoma

- Mostly **unilateral** and grows to **large** size. CA-125 is NOT raised.
- **Pseudomyxoma peritonei** maybe associated.

Dysgerminoma

- **MC malignant** germ cell tumor (GCT) of ovary.
- Also **most radiosensitive** GCT.
- Also GCT with **best prognosis**.
- Homologous to testicular **seminoma**.
- ↑ **hCG, LDH** and **alkaline phosphatase**.
- A/w **Turner's** syndrome.
- Note: GCTs are usually unilateral, BUT dysgerminoma can be **bilateral** in 20% cases.

Endodermal Sinus (Yolk Sac) Tumor

- **Highly malignant** GCT with **worst prognosis**.
- **Rapidly grows** and may present as **acute abdomen**.
- Also seen in **testes** in boys and **sacroccocygeal** area of young children.

- **Schiller Duvall** bodies are seen (*resemble glomeruli*); ↑**AFP** and alpha-1 antitrypsin antibodies.
- **100% unilateral!**

Choriocarcinoma

- Rare, but **malignant**; can develop *during pregnancy* in *mother or baby*.
- Large **hyperchromatic syncytiotrophoblastic** cells.
- A/w **theca-lutein** cysts.

Granulosa-Theca Cell Tumor

- Secretes **estrogen** → **precocious puberty** (children).
- Endometrial hyperplasia/menorrhagia or carcinoma in adults.
- **Call-Exner bodies** on microscopy ('**Call Exner**, for a **Grand party!**').
- Tumor cell nuclei are grooved - '**coffee bean nuclei**'.
- Tumor cells secrete **inhibin B**.

'Catchwords' in Ovarian Tumors Histology

Feature	Associated tumor
Schiller Duvall Body	Endodermal sinus tumor
Call-Exner bodies and coffee bean nuclei	Granulosa cell tumor
Reinke's crystal	Hilus cell tumor
Psammoma bodies	Serous epithelial tumors
Walthard cell nests	Brenner tumor
Signet ring cells	Krukenburg tumor
Hobnail cell	Clear cell tumor
Skin, teeth, cartilage	Dermoid cyst (teratoma)
Rokitansky protuberance	

FIGO Staging of Ca Ovary (2014)

Stage I: Tumor confined to ovaries	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings
IB	Tumor involved both ovaries, otherwise like IA
IC	Tumor limited to one or both ovaries
IC1	Surgical spill (intraoperative capsule rupture)
IC2	Capsule rupture before surgery or tumor on ovarian surface
IC3	Malignant cells in ascites or peritoneal washings
Stage II: Tumor involves one or both ovaries with pelvic extension (below pelvic brim) or primary peritoneal cancer	

Contd...

Contd...

IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
Stage III: Tumor involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
IIIA1	Positive retroperitoneal lymph nodes only IIIA1(i): Metastases < 10 mm IIIA1(ii): Metastases > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement +/- positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic peritoneal deposit < 2 cm +/- positive retroperitoneal lymph nodes. It includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic peritoneal metastases > 2 cm +/- positive retroperitoneal lymph nodes. It includes extension to capsule of liver/spleen
Stage IV: Distant metastases excluding peritoneal metastases	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Treatment

- Just like for Ca endometrium, staging for Ca ovary is done surgically: surgical staging includes **total abdominal hysterectomy (TAH) + Bilateral salpingo-oophorectomy (BSO) + Omentectomy**.
- **Debulking or primary cytoreductive surgery** is the main aim of treatment, especially in advanced disease.
- The main management after staging consists of postoperative chemotherapy: preferred drugs are **cisplatin, carboplatin** and **paclitaxel**.
- **Neoadjuvant chemotherapy** - chemotherapy given prior to surgery to reduce size of tumor.
- **Radiotherapy** has **little role** to play in the adjuvant therapy of ovarian Ca. **Dysgerminoma and granulosa cell** tumors are **radiosensitive**, but not always curable by radiotherapy.

MC in Ovarian Neoplasms

Most common feature	Tumor
MC ovarian tumor overall	Epithelial tumors (90%)
MC benign ovarian tumor	Dermoid cyst (teratoma)
MC malignant ovarian tumor	Serous cystadenocarcinoma
MC ovarian germ cell tumor	Teratoma (dermoid cyst, benign)
MC malignant ovarian germ cell tumor	Dysgerminoma
MC functional ovarian cyst	Follicular cyst
MC ovarian cyst to rupture	Corpus luteal cyst
MC route of spread of ovarian cancer	Transcoelomic (tumor exfoliation) > Lymphatic > hematogenous
MC gene involved in epithelial ovarian tumor	p53
MC complication of ovarian tumor	Torsion
MC tumor to undergo torsion in pregnancy	Dermoid cyst

FALLOPIAN TUBE CANCER

- **Latzko's triad: Pelvic mass, pelvic pain and a serosanguinous vaginal discharge** or vaginal bleeding, vaginal discharge and abdominal pain. Such clinical triads are however found only in 15% of cases.
- The classical symptom of '**hydrops tubae profluens**' which is lower abdominal pain relieved by watery vaginal discharge is diagnostic but present in only 9% of cases.

RHABDOMYOSARCOMA (RMS)

- The two subtypes of rhabdomyosarcoma (RMS) are Alveolar RMS (ARMS) and Embryonal RMS (ERMS).
- Within ERMS subtype, there are two histopathologic variants with superior outcome: botryoid and spindle cell.
- The term ERMS was coined to indicate the microscopical similarity of the tumor cells to developing skeletal myocytes.
- **ERMS** is the MC type of RMS tumors, and usually occurs in **young children** (median age of 6.5 years).
- ERMS often occurs in the **head and neck region, genitourinary tract, and retroperitoneum**.
- **Sarcoma botryoides**:
 - A subtype of ERMS; presents as a **vaginal submucosal lesion** giving the typical '**grape-like**' polypoid appearance

- It is usually seen in **female infants** and **children**.
- Microscopic appearance of a **dense cambium layer** of tumor cells under an intact epithelial surface is seen.
- **Blood stained** watery vaginal discharge is the main symptom.
- Treatment: **Chemotherapy VAC** (Vincristine, Actinomycin, Cyclophosphamide) **followed by surgery** is the treatment of choice.
- Prognosis is **poor** and **recurrence** is common.

GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)

GTN Includes

- Persistent hydatidiform mole
- Invasive mole (chorioadenoma destruens saruens)
- Choriocarcinoma
- Placental site trophoblastic tumor (PSTT)

Important Points about above Conditions

- GTN *after* non-molar pregnancy is **always** a **choriocarcinoma**.
- PSTT is NOT responsive to chemotherapy; **hysterectomy** is the *treatment of choice*.
- **Choriocarcinoma** is a **highly malignant** tumor arising from chorionic epithelium.
- **MC site of metastases** of GTN is to the **lungs**.
- **Chemotherapy** is the *mainstay of treatment* in GTN.

Low-risk (good prognosis) GTN	High-risk (poor prognosis) GTN
<ul style="list-style-type: none"> ▪ Disease is present < 4 months duration ▪ Initial serum hCG level < 40,000 mIU/ml ▪ Metastases limited to lung and vagina ▪ No prior chemotherapy 	<ul style="list-style-type: none"> ▪ Long duration of disease (> 4 months) ▪ Initial serum hCG > 40,000 mIU/mL ▪ Brain or liver metastases ▪ Following term pregnancy ▪ Failure of chemotherapy ▪ WHO score ≥ 7

DEGREES OF PERINEAL TEAR

First degree	Lacerations of hymen, the fourchette, lower part of the vagina, and the perineal skin, but the perineal body remains intact
Second degree	Lacerations of the posterior vaginal wall and varying degrees of tear of the perineal body excluding the anal sphincter
Third degree (complete)	Involves major lacerations of the posterior vaginal wall and tear of the perineal body including the anal sphincter with or without involvement of the anal canal or even the rectum

IDEAL TIMING OF GYNEC PROCEDURES

Test	Timing
Fern test	In pre-ovulatory phase
Post Coital test	On expected day of ovulation
Endometrial biopsy	23–26 days of cycle (pre-menstrual phase)
Tubal patency test/hysterosalpingography	5–12 days of menstrual cycle (pre-ovulatory phase)
Radiological investigation in reproductive age woman	First 10 days of menstrual cycle
IUCD insertion	Within 2–3 days of completion of menses

CULDOCENTESIS

- Culdocentesis is *aspiration of peritoneal fluid* from the *cul-de-sac or pouch of Douglas* (Rectouterine Pouch).
- Indications:
 - In suspected disturbed ectopic pregnancy or other causes producing **hemoperitoneum**.
 - In suspected cases of **pelvic abscess**.

TYPES OF RADICAL HYSTERECTOMY

- **Type 1: Extrafascial or Simple** hysterectomy (removal of cervix + corpus BUT NO mobilization of ureter and NO removal of parametria)
- **Type 2: Modified (Wertheim's)** radical hysterectomy (Type 1 + Structures removed include: central portion of parametrium; medial half of uterosacral and cardinal ligaments; 1-2 cm of upper vagina; pelvic and para-aortic lymph nodes)
- **Type 3: Meig's** radical hysterectomy (Type 2 + wide excision of uterosacral and cardinal ligaments and 2-3 cm of upper vagina; take care to PRESERVE superior vesical artery)
- **Type 4: Extended** radical hysterectomy (extensive dissection of ureter from vesicouterine ligament; **sacrifice** of superior vesical artery and removal of upto 75% of vagina)
- **Type 5:** Type 4 + removal of involved portions of bladder and ureter.

MORE INSTRUMENTS IN GYNECOLOGY

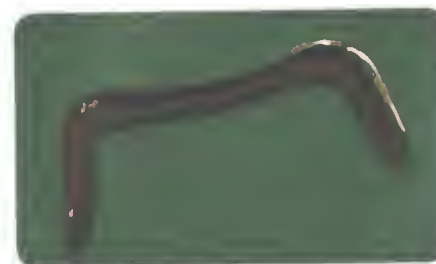


Fig. 25.17: Sim's speculum used to retract posterior vaginal wall

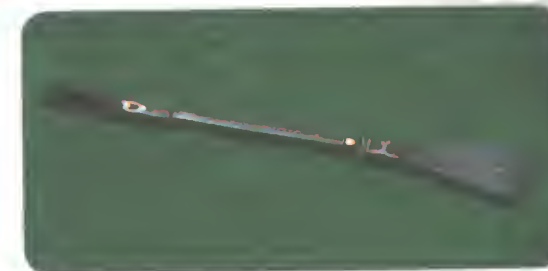


Fig. 25.21: Uterine curettes sharp and blunt curette



Fig. 25.18: Cusco's self retaining bivalved speculum used in OPD for examining vagina and cervix; can also be used for minor procedures like IUCD insertion, colposcopy, etc.



Fig. 25.22: Endometrial biopsy (EB) curette



Fig. 25.19: Thudicum's nasal speculum used to inspect vagina in children/young girls



Fig. 25.23: Vulsellum used to hold anterior lip of cervix



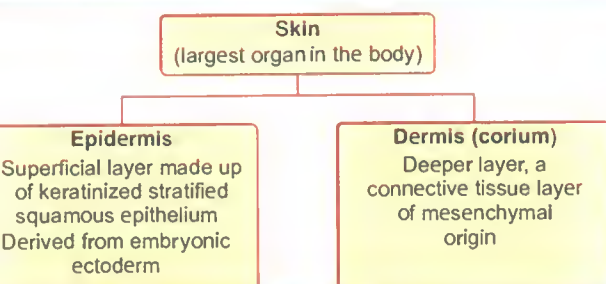
Fig. 25.20: Cervical dilators



Fig. 25.24: Allis forceps

Dermatology

THE SKIN



THE EPIDERMIS (FIG 26.1)

Germinative zone

Stratum basale/Stratum germinativum: Basal cell layer with *intense mitotic activity* of keratinocytes; this layer also contains *melanocytes*, *Merkel cells*.

Stratum spinosum (prickle cell layer): Superficial to the basal layer; it contains keratinocytes that are linked by *prominent desmosomes* appearing like spines (hence *prickle cell layer*); this layer provides *mechanical coherence* of epithelium. Keratinocytes contain *housekeeping arganelle*.

Note: Stratum *Malpighi* = stratum spinosum + stratum basale together

Zone of keratinization

Stratum granulosum: Consisting of flattened cells with pyknotic nuclei surrounded by the keratin precursor *keratohyalin* that is made up of *histidine rich protein* or *profilaggrin*, *loricrin* and *involucrin* (involucrin is upregulated in *psoriasis*). *Lamellar granules* (Odland bodies or *keratinosomes*) are present in the cytoplasm of cells of the upper spinosum layer and granulosum layer. This layer forms *water impermeable barrier*. *Absence* of this layer is seen in *psoriasis* and *ichthyosis vulgaris*.

Stratum lucidum: Also known as *clear layer* since cell boundaries are extremely indistinct and contains *degenerated keratinocytes*. This layer is prominent *only* in heavily keratinized areas such as *glabrous (hairless) skin of palms and soles* and contains the keratin precursor *eleidin*.

Stratum corneum: *Thickest layer* of epidermis; most superficial layer of the epidermis; consists of flattened squames, the remnants of cells, which have become completely filled with keratin and are *anucleate*. The 'dead cells' are held together by a layer of lipid (synthesized in the stratum spinosum), which makes this layer highly *waterproof*; *prematures (VLBW neonates)* have poorly developed stratum corneum.

EXTRA EDGE

- Mnemonic: Base to top layer - '*B*eautiful *S*exy *G*irl *L*ikes *C*orn!'
- The epidermis derives nutrition entirely by diffusion from capillaries in the dermal papillae.
- Three main surface markings on the epidermal surface: *Tension lines*, *Flexure lines* and *Papillary ridges*.
- Papillary ridges are confined to the palmar surface of the hands, and soles of the feet including the digits—responsible for *fingerprints*.
- *Stratum spinosum* is the *thickest layer* of epidermis and contains *maximum desmosomes*

Adhesions in the Epidermis

- **Desmosomes**
- Provide *adhesion between adjacent keratinocytes*. They contain three proteins
 - *Desmoglein*: Destroyed in staphylococcal scalded skin syndrome (SSSS), IgG Pemphigus and Bullous impetigo
 - *Desmoplakin*: Destroyed in IgA pemphigus
 - *Desmocollin*: Destroyed in paraneoplastic pemphigus.
- **Hemidesmosomes:** Connects basal *keratinocytes* to *basement membrane*; contain Bullous pemphigoid antigen 2 (BPAG2) and BPAG1.

Special Cell in Epidermis

Keratinocytes

- These cells contain *keratin*.
- *95% of epidermis* is made of keratinocytes. It is the only *original resident* of epidermis whereas all other cells mentioned below are *immigrants*!
- Keratohyalin granules contain *filaggrin* which intermingles keratin filaments and provided *more strength*.
- Maximum keratin is in the stratum corneum and least in stratum basale.
- There is a change in keratin filaments (K) from basal to upper layers. *K5 and K14* in *basal layer* (mutations cause *epidermolysis bullosa simplex*); *K1 and K10* in *suprabasal layers*.

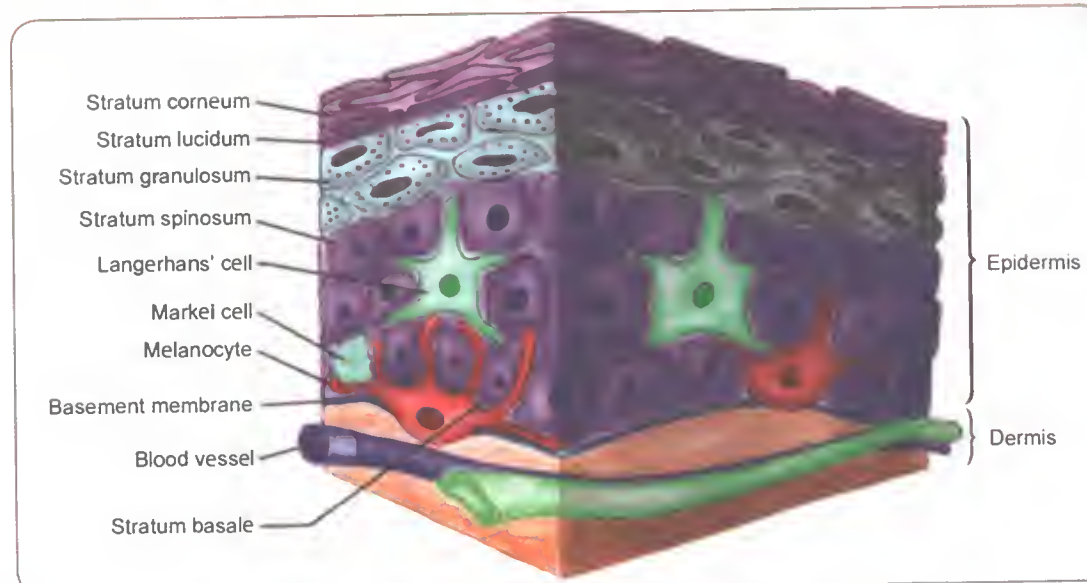


Fig. 26.1: Histology of skin

Melanocytes

- *Neural crest* derived cells.
- These are *dendritic* cells that migrate to the *basal layer* of epidermis during *embryogenesis*.
- They synthesize melanin and *protect skin* from *UV light*.
- *Eumelanin* (brown/black pigment) present in dark skin and *Pheomelanin* (yellow/red pigment) present in Caucasian skin.
- *Skin color* is dependent upon (i) degree of melanization of melanosomes, (ii) their size, number and distribution in the epidermal melanin unit (*NOT* due to the number of melanocytes).
- **Epidermal-Melanin Unit:** One melanocyte is surrounded by about *36* keratinocytes (*1:36*).

Langerhans' cell

- *Bone marrow*-derived, *antigen-presenting* dendritic cell
- Found chiefly in the *stratum spinosum*
- They contain *tennis racquet shaped 'Birbeck granules'*

Merkel's (Tastzellen) cells

- *Ectodermal* derived *non-dendritic neuroendocrine* cells found chiefly in hairy skin
- Present in the *stratum basale*; contains surface *microvilli* and *desmosomes*.
- These are *slow adapting type 1 mechanoreceptors* sensitive to *pressure*

- *Cytokeratin 20* is a marker for oral and cutaneous Merkel cells.

DERMIS

- Very *THICK* Dermis = *palms* and *soles*; thicker on the *posterior aspect* of the *body*, and *lateral sides* of the *limbs*.
- Very *THIN* Dermis = eyelids, scrotum and penis.
- Dermis includes collagen of types *I and III* (70–80%).
- **Superficial papillary dermis**
 - Includes the *dermal papillae* (wavy projections of the dermis upwards into the epidermis), which are best developed in the thick skin of the *palms and soles*;
 - Contains *Oxytalan* fibers (small elastic fibers).
- **Deep reticular dermis**
 - Consists of bundles of collagen fibers and some yellow elastic fibers, which are arranged *parallelly*.
 - Directions taken by these parallel bundles vary in different parts of the body = *cleavage lines* of the skin—arranged longitudinally in limbs; horizontally in the trunk and the neck.
 - *Surgical incisions* along cleavage lines heal with *minimum scar* formation.
- **Wrinkling** of skin: *Yellow elastic fibers atrophy* and the skin becomes wrinkled with aging.
- **Striae** (e.g. linea gravidarum of pregnancy): White streaks on skin due to partial atrophy of fibers in the reticular dermis.

SUBCUTANEOUS FAT (PANNICULUS)

- The subcutaneous tissue serves as a depot for **fat storage**.
- Subcut tissue contains numerous **mast cells**—rupture of mast cells in **subcut fat** causes **angioedema**. (ALSO know - rupture of mast cells in **dermis** causes **urticaria**).
- Panniculus adiposus** is the fatty layer of the subcutaneous tissues (**absent in** penis, scrotum and eyelid).
- Panniculus carnosus** is a deeper vestigial layer of muscle - represented in the adult as three subcutaneous muscles (**platysma, dartos and palmaris brevis**).

More MCQ Points

- **Epidermal renewal time** = Time elapsing between the formation of a keratinocyte in the basal layer of the epidermis and its shedding from the surface of the epidermis; it is highly variable - about **50–60 days**.
- **Reduced** epidermal turnover time - in **psoriasis** (only 10 days!).
- **Epidermal stem cells** are present in (**HIS**)
 - Hair follicle bulge;
 - Interfollicular epidermis and
 - Sebaceous gland (base)

SKIN LESIONS**Primary Skin Lesions**

- MACULE:** A **flat, well circumscribed** change in the skin color < **1 cm**; a macule > **1 cm** = '**patch**'.
- PAPULE:** A solid **raised** lesion that has distinct borders and is < **1 cm** in diameter; papule > **1 cm** = '**plaque**'.
- NODULE:** Large palpable papule that extends **2 cm vertically** into the dermis or subcutaneous tissue; > **2 cm** extension is called a **tumor**.
- VESICLE:** **Fluid filled epidermal** lesions < **1 cm** in diameter; if > **1 cm** in dia, it is called **bulla** (maybe flaccid or tense).
- PUSTULE:** Circumscribed elevated lesions that contain pus. They are most commonly infected (as in folliculitis). **Sterile** pustules maybe seen
 - 'Lakes of pus' as in generalized **pustular psoriasis** of von Zumbusch;
 - '**Hypopyon sign**' as in **bullous pemphigoid** and subcorneal pustular dermatosis (**SCPD**) - horizontal pus level within blister cavity.
- WHEAL:** A **transient** area of edema in the upper epidermis; classical of **urticaria**.

Secondary Skin Lesions

- Scale:** Abnormal thickening of the skin surface and formation of scaly white lamellae from the accumulation of horny cell layers.

Type of Scale	Condition
Silvery/mica like scales	Psoriasis
Yellow/greasy scales	Seborrheic dermatitis
Collarette scales	Pityriasis rosea
Leaf-like scales	Pemphigus foliaceus
Powdery/branny fine scales	Pityriasis versicolor
Fish-like scales	Ichthyosis vulgaris
Wickham's striae (lacy white)	Lichen planus

- Crust:** Crust is solidified keratin and exudate that forms on an erosion or on ulcerous skin. A crust of clotted blood is called a bloody crust (commonly called a scab).
 - **Honey color crust** - **non-bullous impetigo**
 - **Hemorrhagic crust** - Toxic epidermal necrolysis (**TEN**)
- Excoriation:** Is partial damage to the epidermis by injury or rubbing/scratching.
- Erosion:** Raw lesion due to loss of epidermis only - hence **NO scar**. It often develops after breakage of a blister or pustule.
- Ulcer:** An ulcer is the complete deficiency of **epidermis and dermis** - heals **with scars**.
 - **Undermined ulcer:** Cutaneous TB, chancroid, pyoderma gangrenosum
 - **Punched out/trophic ulcer:** Seen in peripheral neuropathy (DM, Hansen's)
 - Ulcer with **Rolled/Pearly/Beaded** edge: Rodent ulcer (Basal cell Ca).
- Fissure:** Is a thin **linear** cleavage running through the deep epidermal layer and the dermis. It is commonly called a **crack**.
- Atrophy:** Skin becomes thin or has a smooth or nely wrinkled surface.
- Scar:** A scar is the reactive proliferation of dermal collagen after the skin is injured.
- Sclerosis:** Diffuse or circumscribed hardening of skin due to **dermal fibrosis**.
- Lichenification:** Lichenification is the thickening and hardening of skin.

TERMS IN DERMATOPATHOLOGY

- Acanthosis:** Increase in thickness of **stratum spinosum** due to stimulation of basal layer. Seen in **viral** infections,

chronic epidermal inflammations (**psoriasis, lichen planus, eczema**) and conditions where keratinocytes separate from each other (**pemphigus, Darier's disease**).

- Hyperkeratosis:** **Thickened** stratum corneum.
- Parakeratosis:** Presence of immature **nucleated cells** in the **stratum corneum**; maybe a **normal finding on mucous membranes**. Also seen in **Psoriasis, Actinic keratosis** and **Bowen's disease**.
- Orthokeratosis:** **Hyperkeratosis without parakeratosis** (seen in **lichen planus**).
- Acantholysis:** **Loss of coherence** between epidermal keratinocytes.

Primary acantholysis	Secondary acantholysis
Due to rupture of desmosomes leading to circular keratinocyte with enlarged nucleus and perinuclear halo and absent nucleoli (Acantholytic cell)	Ballooning of keratinocyte is the main problem leading to acantholytic cell (NOT ruptured desmosomes)
Seen in (PHD's)	Seen in
<ul style="list-style-type: none"> • Pemphigus • Hailey Hailey dis • Darier's dis • SSSS 	<ul style="list-style-type: none"> • Viral infections (Herpes)

- Dyskeratosis:** **Premature** keratinization in the **lower epidermis below** the level of **stratum granulosum**. Dyskeratosis is often a/w **acantholysis**.

- **Corps Ronds:** Acantholytic, dyskeratotic, basophilic cells with have round nuclei with a perinuclear halo in basal epidermis.
- **Corps Grains:** Similar cells with elongated 'grain' shaped nucleus in upper epidermis.
- **Dyskeratosis with corps ronds/grains** classically seen in **Darier's disease**. Also seen in **Grover's disease, Hailey-Hailey disease** and **warty dyskeratoma**.
- Foam cell:** A lipid-laden macrophage.
- Hydropic degeneration** of basal cells: Aka **liquefaction degeneration**, it is a type of degeneration causing **vacuolization of the basal cells** may lead to pigment incontinence. It is seen in **SLE, dermatomyositis**, and in early **lichen planus**.
- Spongiosis:** **Intercellular edema** of the epidermis (of **stratum spinosum**) which may progress to vesicle formation in the epidermis—seen in **eczema**.
- Pigment incontinence:** The deposition of melanin in the dermis, which when not in association with a pigmented lesion **implies prior basal layer damage**.

Signs in dermatology

Sign	Seen in	Remarks
Antenna sign	Kerotosis Piloris	Individual follicles show a long strand of keratin glistening in tangentially incident light
Auspitz sign	Psoriasis	Pinpoint bleeding on removal of scales
Branham's sign; Nikoladoni's sign	Arteriovenous fistula	Slowing of heart rate in response to manual compression
Breakfast, lunch and dinner sign	Bites of bedbugs (Cimex lectularius)	Bites usually follows a linear pathway in a group of 3–5 blood meals
Chandelier's sign	Gonorrhea	Ascending gonorrhea in women involving cervix, endometrium and tubes (palpation causes severe pain and women jump up and reach for the chandelier!)
Carpet tack's sign	DLE, seborrheic dermatitis	Undersurface of the adherent scale of DLE shows patulous hair follicles
Cerebriform tongue sign	Pemphigus vegetans	Pattern of sulci and gyri over dorsum of the tongue
Coup'd'ongue sign	Tinea versicolor	Loosening of scales by scratching with fingernail
Coudability sign	Alopecia aerata	Exclamation mark shaped hairs in perilesional hair bearing skin which kink easily
Darier's sign	Urticaria pigmentosa (systemic mastocytosis)	Rubbing and heat/bathing cause localized urticaria
Pseudo-Darier's sign	Congenital smooth muscle hamartoma and Becker's nevus	Stroking causes transient induration with piloerection

Contd...

Signs in dermatology		
Sign	Seen in	Remarks
Dimple sign; Fitzpatrick sign	Dermatofibrosarcoma protuberans	Dimpling of skin with lateral pressure
Dory Flop sign	Syphilis	Syphilitic chancre in an uncircumscribed male
Dubois sign	Congenital syphilis	<i>Short little finger</i>
Higoumenaki's sign	Congenital syphilis	Thickened sternal portion of clavicle
Buschke-Ollendorff sign	Secondary syphilis	Papule is very tender to touch
Flag sign	Kwashiorkor	Sharply demarcated alternating bands of pigmented and depigmented as well as thicker and thinner hair, evidence of intermittent malnutrition.
Forchheimer sign	Rubella	Enanthema on soft palate
Groove sign	Lymphogranuloma venereum (LGV)	Due to separation of the enlarged inguinal and femoral lymph nodes by the inguinal ligament
Head light sign	Atopic dermatitis	Perinasal and periorbital pallor
Hamburger sign	Trichotillomania	Vertically split hairs with RBCs and proteinaceous material in the split
Hanging curtain sign	Pityriasis rosea	When skin is stretched across the long axis of the herald patch, scale is notes to be finer, lighter and attached at one end, which tends to fold across the line of stretch
Hertoghe's sign: aka Queen Anne's sign	Atopic dermatitis, hypothyroidism, syphilis, HIV, DLE, trichotillomania	Loss of lateral third of eyebrows
Homan's sign	Deep vein thrombosis	Pain in back of calf or knee when the foot is dorsiflexed
Barnett's sign	Scleroderma neck sign	Tightening of skin of neck on extending the head
Ingram sign	Systemic sclerosis	Inability to retract lower eyelid
Leser tretlat, sign	Sign of internal malignancy	Appearance of large number of seborrheic keratoses
Lovibond profile sign, Lovibond angle	Clubbing	Angle located at the junction between the nail plate and proximal nail fold, and which is normally less than 160 degrees. In clubbing, the angle exceeds 180 degrees
Milian's ear sign	Erysipelas	Erysipelas can spread into the pinna (being cuticular infection), whereas cellulitis cannot spread to the pinna due to close adhesion of skin to cartilage of ear (without any areolar tissue)
Nose sign (Pavithran's nose sign)	Exfoliative dermatitis	Sparing of the nose
Oil drop sign	Psoriasis	Discoloration of nail bed
Osler's sign	Alkaptonuria	Blue-black pigmentation near recti muscle insertions
Crowe's sign	Neurofibromatosis	<i>Axillary freckling</i>
Button hole sign	Neurofibromatosis	Neurofibroma can be invaginated with tip of index finger and reappears on release of pressure
Patrick Yesudian sign	NF-1	<i>Palmar freckling</i>
Pillow sign	Netherton's syndrome	Hair shaft defect patient sees hair on pillow on getting up in the morning

Contd

Contd...

Signs in dermatology		
Sign	Seen in	Remarks
Prayer sign	Diabetic cheiroarthropathy	Patient inability to completely close gaps between opposed palms and fingers when pressing their hands together in prayer position.
Promontory sign	Kaposi's sarcoma, angiosarcoma	Histopath finding of a blood vessel protruding into abnormal vascular space
Punchi's sign	Vitiligo	White color of vitiligo turns red during menstruation and returns to normal later
Racoon's sign (Panda's sign)		<i>Periorbital ecchymoses after basal skull fracture</i> ; also <i>postproctoscopic periorbital purpura in amyloidosis</i> ; Erythematous eruption in periorbita in neonatal lupus erythematosus
Reverse namaskar sign	Ehler's Danlos	Patient doing 'namaskar' behind his back
Gorlin's sign	Ehlers Danlos	Patients can touch tip of nose with tongue
Romana's sign	T cruzi; Chaga's disease	Swelling near eye where the reduvid bug bite has occurred
Rusell's sign	Bulimia nervosa	<i>Crusted callosity on knuckles</i> of dominant hand due to repeated self induced vomiting
Samitz sign	Dermatomyositis	Dystrophic and ragged cuticle
Shawl sign	Dermatomyositis	Erythema over the upper back and shoulders
Toy soldier sign	Mycoses fungoides	Linear aggregation of neoplastic lymphocytes along the dermoepidermal junction in histopath
Wartenberg's sign	Ulnar nerve paralysis due to leprosy	The little finger is in constant abduction and maybe the earliest sign of ulnar nerve affection

Microabscesses

- **Munro's microabscesses:** Collection of neutrophils in stratum **corneum** in **psoriasis** (also in *seborrheic dermatitis*).
- **Spongiform pustules of Kogoj:** Collection of neutrophils in stratum **spinosum** in psoriasis. ALSO seen in *Reiter's disease, geographic tongue* and rarely in *candidiasis*.
- **Pautrier microabscesses:** Collections of 3 or more *atypical T lymphocytes* within the epidermis (stratum **spinosum**) in **mycosis fungoides** (*cutaneous T cell lymphoma*).

- **Grenz zone:** It is a free area of uninvolved dermis between the epidermis and the upper edge of a dermal lesion (inflammatory or neoplastic infiltrate). 'Grenz' = 'border/frontier' in German.
 - **Clear Grenz zone** is seen in **granuloma faciale, lepromatous leprosy**, lymphocytoma cutis, intradermal nevus, colloid milium, **dermatofibroma**, acrodermatitis chronica atrophicans.
 - Grenz zone is **absent/involved** in **dermatofibrosarcoma protuberans, tuberculoid leprosy**.

PSORIASIS

- **Etiology:** A/w **HLA CW6** +ve family history in >50% patients; Affects 1–2% of the world's population.
- **Pathogenesis:** MC abnormality is **increased epidermal proliferation** rate. In normal skin 27 days. In psoriatic skin **4 days**.
- **Histology (Fig. 26.2)**
 - **Parakeratosis** (stratum corneum contains *nuclei*).
 - **Acanthosis** occurs (increase in thickness of *stratum spinosum*).
 - **Munro's microabscesses:** Collection of neutrophils in stratum **corneum**.
 - **Spongiform pustules of Kogoj:** Collection of neutrophils in stratum **spinosum**.
 - **'Squirting' papillae:** Migration of neutrophils out of dilated dermal capillaries.
 - **Suprapapillary thinning** with thin epidermis above edematous dermal papillae.
 - Exaggeration of dermal **rete** pattern.
 - **Absent granular** layer.

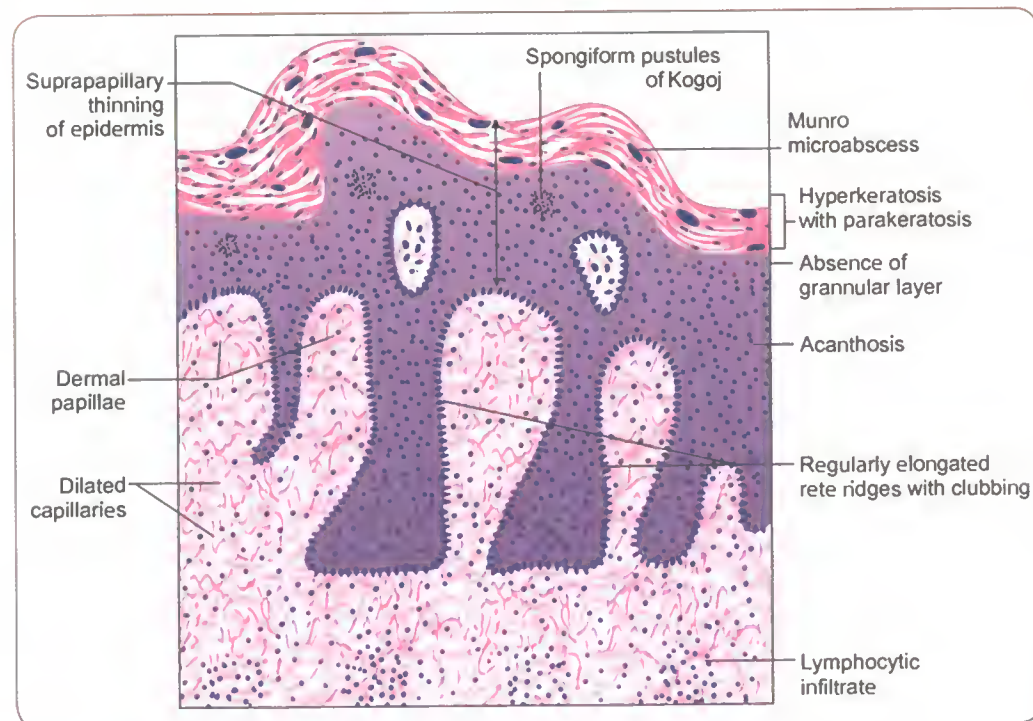


Fig. 26.2: Psoriasis. Diagrammatic histopathological findings



Fig. 26.3: Psoriasis: red scaly plaques involving the extensors of the legs and knees

- **Clinically**
 - Chronic inflammatory skin disorder characterized by **erythematous, sharply demarcated** papules and round plaques, covered by **silvery mica like scales**. (Note that scales of psoriasis are typically **absent in groin and flexures**).
 - MC age of onset is **second and third decade**.
 - Common sites are **extensor aspect** of elbows, knees, hands (**knuckles**); **scalp** and **sacral area** and nails.
 - The skin lesions of psoriasis are **variably pruritic**.

Presentation and Types of Psoriasis

- **Stable Plaque Psoriasis (psoriasis vulgaris)**
 - **MC type** of psoriasis.
 - Common sites are **extensor aspect** of elbows, knees, hands (**knuckles**); **scalp** and **sacral area**, napkin area (in infants – can present as ‘nappy rash’) and nails.
 - **Rupoid psoriasis**: Limpet-like cone-shaped hyperkeratotic lesions of psoriasis.
- **Guttate (Eruptive) or Raindrop Psoriasis**
 - More common in **children and adolescents**, frequently preceded by **streptococcal sore throat** infection.
 - Antistreptococcal **antibiotics** may be necessary.
 - **Self resolving** quite rapidly (**tonsillectomy** had been tried!)

Aggravating factors

- Pregnancy
- Sepsis; Stress (emotional); Shivering (cold injury/winter), Streptococci
- Trauma.
- **Drugs**: Beta-blockers, lithium; antimalarials (chloroquine); NSAIDs (ibuprofen); sudden stoppage of systemic steroids.

- Also responds rapidly to **UV-B**.
- **Erythrodermic Psoriasis**
 - Skin becomes universally **red and scaly** and **>90%** of body gets involved.
 - **Shivering** compensates for the considerable heat loss
 - Erythroderma may be **initiated by** the irritant effect of tar or dithranol or by systemic/topical steroid withdrawal
 - **Methotrexate** is the **DOC**; others are Cyclosporine (for life-threatening erythroderma) and Acitretin.



Fig. 26.4: Erythrodermic psoriasis in a college student

- **Inverse or Seborrheic Psoriasis**
 - Classical lesions on scalp a/w less typical moist lesions in **body folds** (groins, axillae, submammary region, navel); **NO** visible scales; can be **very resistant** to therapy.
 - **No alopecia** occurs.
- **Pustular Psoriasis**
 - Rare but **serious** type of psoriasis, maybe precipitated by **sudden stoppage of steroids** (hence oral steroids are NOT used in psoriasis); sudden onset with small **sterile pustules** on an erythematous base; **palms and soles** maybe involved (acrodermatitis pustulosa – more common in smokers).

Subtypes of pustular psoriasis

- **von Zumbusch** Psoriasis: Combination of erythroderma + sterile pustular psoriasis (**lakes/sheets** of pus!)
- **Impetigo herpetiformis**: Generalized **pustular psoriasis of pregnancy**; a/w hypoparathyroidism and hypocalcemia
- **DOC** for pustular psoriasis: **Acitretin** (retinoids). Others are cyclosporine and methotrexate.
- **DOC** for impetigo herpetiformis: **Corticosteroids**; cyclosporine in refractory cases (MTX and retinoids are **contraindicated** in pregnancy).
- Biologicals (TNF alpha inhibitors are second choice).

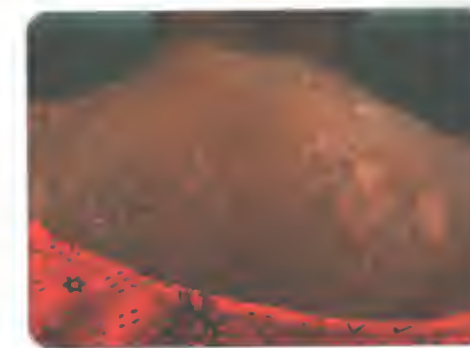


Fig. 26.5: Acute generalized pustular psoriasis of von Zumbusch



Fig. 26.6: Impetigo herpetiformis: superficial pustules at the periphery of an erythematous lesion. Pustular psoriasis of pregnancy

EXTRA EDGE

- **Parapsoriasis** is a term used for well-defined maculopapular erythematous lesions that occur in **middle and old age**; some cases undoubtedly develop into **mycosis fungoides**.

Signs in psoriasis

- **Woronoff's ring**: Whitish halo around the lesion
- **Grattage test**: On scratching the lesion mica like scales appear.
- **Bulkeley's membrane**: Removal of scales reveals a glistening red membrane of Berkeley.
- **Auspitz sign**: When scales are forcefully removed, pinpoint bleeding from dilated superficial capillaries occurs through Bulkeley's membrane (**ABSENT** in pustular psoriasis).
- **Candle-grease Sign (Tache de bougie)**: When a lesion is scratched with the point of a dissecting forceps, a candle-grease-like scale can be repeatedly produced even from the non-scaling lesions.
- **Koebner/isomorphic phenomenon**: Traumatized areas (scratching, wounds, hat band pressure, sunburn) develop lesions of psoriasis; also seen in **lichen planus** and **vitiligo**.



Figs. 26.7A and B: Psoriasis (grattage test). A. Burkle's membrane; B. Auspitz's sign



Fig. 26.8: Sign of the candle stain: A typical psoriatic plaque which shows an increased prominence of scaling upon being scratched with a glass slide. This gives the appearance of a scratched wax candle



Fig. 26.9: Woronoff's ring is a faint ring of hypopigmentation seen around the resolving lesions of psoriasis. Here there is also an erythematous area around the hypopigmented ring

Psoriasis of Nails

- **'Thimble Pitting'** is MC due to involvement of proximal nail matrix.



Fig. 26.10: Pitting of nail in psoriasis

- **Onycholysis** (separation of nail from nail bed)
- **Subungal hyperkeratosis** (excess accumulation of keratin on the nail bed)
- **'Oil drop' sign:** Translucent yellow-red discoloration in nail bed (salmon patch) resembling an oil-drop.
- **Note:** A higher incidence of arthritis is seen in those with psoriatic nail changes.

Psoriatic Arthritis

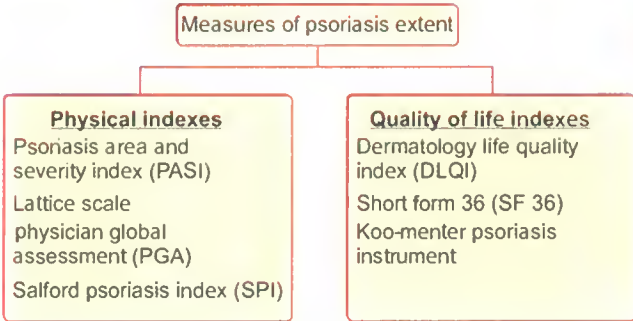
- 30% patients of psoriasis have psoriatic arthritis; *skin changes precedes joint disease.*
- **Nail changes** occur in almost 90% of PsA.
- **CLASSification criteria for Psoriatic ARthritis = CASPAR.**
- Psoriatic Arthritis features include:
 - Distal interphalangeal joint (**DIP**) predominant
 - Dactylitis (**sausage digits**)

- **Sacroiliitis** (HLA B27 positive)
- **Arthritis mutilans** (severe destructive arthritis).

X-ray signs in psoriatic arthritis

- **'Pencil in cup'** appearance (tapering of the proximal phalanx and bony proliferation of the distal terminal phalanx).
- **'Opera glass hand'** (*main en lignette*—telescoping of one bone into its neighbor with shortening of digits).
- Marginal erosions with adjacent bony proliferation (**'whiskering'**).

Measures of Psoriasis Extent



Treatment of Psoriasis

Topical therapy (if < 10% body surface area involved)

- Vitamin D3 analogues (Calcipotriol or calcitriol)
- **Tazarotene** (topical retinoid)
- Anthralin
- Calcineurin inhibitors (**tacrolimus**) for **face** and intertriginous areas
- Coal tar
- Very weak topical steroids

Phototherapy with oral or topical psoralens (if 10–30% involvement)

- **Goeckerman** regimen (coal tar + UVB lights)
- **Ingram** regimen (Coal tar _ UVB light + anthralin)
- **PUVA** (Psoralens + UVA light): Systemic PUVA; Topical PUVA; Bath PUVA
- Narrowband and broadband UVB therapy
- **Balneotherapy** (Bath with concentrated NaCl solution follow immediately by UVB therapy)
- **308 nm Excimer** laser

Systemic therapy (if > 30% involved)

- **Retinoids (Acitretin)**
 - **DOC** for **pustular** psoriasis
 - **DOC** for **psoriasis in HIV**
 - Side effect: Dyslipidemia, liver abnormalities

- **Methotrexate**
 - **DOC** for psoriatic **arthritis**
 - **DOC** for **erythrodermic** psoriasis
- **Cyclosporine** (calcineurin inhibitor)
 - Useful in **life threatening erythroderma**
- Systemic **Steroids**
 - **DOC** for **impetigo herpetiformis** in pregnancy

Biologics (Immunomodulators)

Useful for psoriasis not responding to conventional medicines

- **TNF inhibitors:** Etanercept; adalimumab; infliximab
- **IL 12/23** monoclonal antibodies: **Ustekinumab**
- **Anti IL-17** antibody: **Ixekizumab, Brodalumab**
- T cell modulators: **alefacept, efalizumab** (withdrawn due to occurrence of **Progressive Multifocal Leukoencephalopathy**)

EXTRA EDGE

- Oral psoralens have to be taken **2 hours prior** to exposure to UV light.
- UV light therapy is **contraindicated** in patients receiving cyclosporine and should be used with great care in all immunocompromised patients due to an increased risk of developing skin cancers (**squamous cell Ca**).
- Other **major indications for PUVA:** Vitiligo, Atopic dermatitis; Polymorphous Light Eruption, Mycosis fungoides.

LICHEN PLANUS

- **'5Ps'** = lesions are **Pruritic** (itchy), **Plain** (flat) topped, **Polygonal**, **Purple** (violaceous), **Papules**.
- Cell-mediated immune response of unknown origin.

Associations

- A/w **hepatitis C** infection
- **Drugs:** gold, antimalarials, diuretics, penicillamine, phenothiazines
- Allergy to **mercury** in **dental amalgam** (risk of **oral LP**)
- Chronic **GVHD** (graft versus host disease).



Fig. 26.11: Purple lesions of LP

Clinically

- Common sites: **inner** aspects of **wrists and ankles**, **flexor** aspect of **forearms**, **shins**, **lower back** (lumbar region), **genitalia** (as annular white lesion), **oral mucosa** (as white **reticular/lacelike** eruption).
- **Wickham's striae**: Fine network of gray/white lines on the lesions.
- **Koebner's** phenomenon: New lesions may appear at the site of trauma.
- Malignant transformation (**squamous cell Ca**) - in oral, genital and esophageal LP.
- **Vulvar** lesions can be pruritic and **painful**.
- Residual **hyperpigmentation** and **scarring** can occur.
- **Morphological types** of LP:

- Lichen planopilaris/follicular LP (**scarring alopecia** on scalp may result);
- Others: **Hypertrophic LP**; **LP pigmentosus**; **Annular LP**; **Bullous LP**; **Ulcerative LP**; **Atrophic LP**; **Actinic LP**; **Linear LP**.
- **Nail changes**:
 - Nail plate **thinning** (**MC finding**) causing longitudinal grooving and ridging.
 - Rarely, the nail matrix can be permanently destroyed with prominent **dorsal pterygium** formation (most **classical**).
 - **20-nail dystrophy (trachyonychia)**: Other causes of trachyonychia are **alopecia aerata** and **psoriasis**.
 - Hyperpigmentation, subungual hyperkeratosis, onycholysis, longitudinal melanonychia.

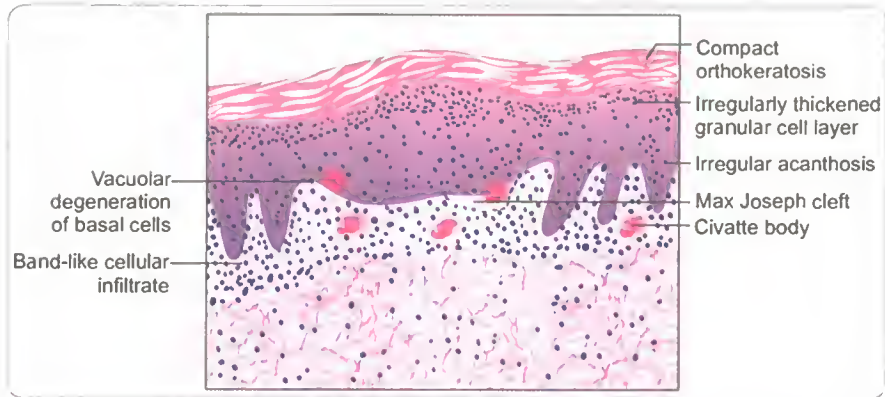


Fig. 26.12: Lichen planus. Diagrammatic histopathological findings

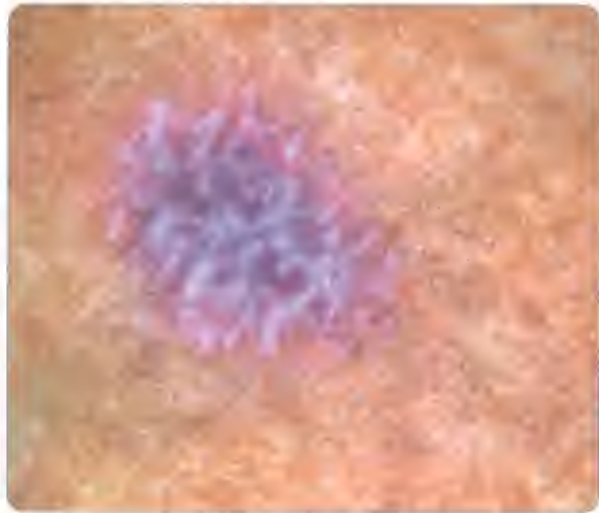


Fig. 26.13: Classical manifestation of LP: Wickham's striae

Courtesy: Dr Bela Shah

Histopathology of LP

- Confirmation of diagnosis is by skin biopsy
- **Basal cell degeneration** (forming '**colloid**, **Civatte** bodies', 'hyaline or cytoid' in the epidermis)
- Heavy T-lymphocyte infiltration in the upper dermis ('**sawtooth**' rete ridges)
- '**Interface** dermatitis'
- **Acanthosis**; **hyperkeratosis**; **orthokeratosis** (i.e. hyperkeratosis without parakeratosis) and a **prominent granular** layer (wedge-shaped hypergranulosis)
- '**Liquefactive degeneration**' of the basal layer
- **Pigment incontinence** (responsible for postinflammatory hyperpigmentation)
- **IgM** on the colloid body surface gives '**bunch of grapes**' on immunofluorescence
- **Max Joseph space**: Subepidermal clefts formed by acantholysis or hydropic degeneration of basal cells

Treatment

- **Spontaneous resolution** occurs in **6 months to 2 years**
- **Topical glucocorticoids** are the mainstay of therapy
- Antihistamines are used for **pruritus**
- Phototherapy (PUVA) maybe used
- **Oral LP** is more **difficult to treat** and typically lasts longer than skin LP; Hydroxychloroquine is used for oral LP.

EXTRA EDGE

- Other causes of **Interface Dermatitis**:
 - Erythema multiforme
 - GVHD
 - Steven Johnson's syndrome (SJS); Toxic epidermal necrolysis (TEN)
 - SLE, dermatomyositis

LICHEN NITIDUS

- Lichen nitidus is a **variant of lichen planus** which presents with closely **grouped, pinhead sized, whitish**, tiny-flat or dome shaped **micropapules** on the **shaft of penis**, **neck**, **dorsal forearms** and **hands**.
- Affects children, young adults; asymptomatic (**NO itching**), Koebner phenomenon maybe seen.
- Histology shows focal granulomatous infiltrate (histiocytes and lymphocytes) - the '**ball**', embedded in the epidermal collarette - the '**claw**' - '**ball in claw**' appearance.
- **NO** treatment needed; **self limiting** and heals with **hyperpigmentation**.



Fig. 26.14: Lichen nitidus: small grouped shiny papules on shaft of penis

PITYRIASIS ROSEA

- **Pityriasis** = fine scales; **rosea** = rose colored or pink; **10-35** years age range; MC in **women**; MC in **spring/autumn**.
- Etiology:
 - **HHV-7 > HHV-6**.
 - **Drugs**: **ACE inhibitors**, Imatinib, Interferon, Ergotamine.
- First manifestation is a **solitary, salmon-pink, annular plaque**, 2-6 cm in diameter ('**Herald**' or '**Mother**' patch), usually on the **trunk**; in few days several small salmon colored macules or patches mainly on the trunk occurs (also on the neck, thighs).
- The **collarette scales** (delicate peripheral trailing scale, cigarette-paper scale) is **attached on the outer border and free on the inner border** of the lesions.
- **Hanging Curtain** Sign: When skin is stretched across the long axis of the herald patch, scale is noted to be finer, lighter and attached at one end, which tends to fold across the line of stretch.
- Lesions on the back are parallel to the ribs giving a '**Christmas tree**' distribution.
- Lesions resemble that of **secondary syphilis** but unlike in syphilis, **palms and soles** are **NOT** involved.
- Moderately pruritic; **self-limiting** in 4-10 weeks.
- (**CHR**istmas = **CHR**istmas, **HER**ald, **RO**sea).

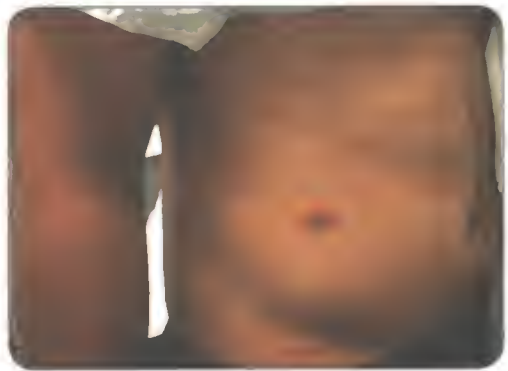


Fig. 26.15: Herald patch in pityriasis rosea

PITYRIASIS RUBRA PILARIS

- Reddish-orange **perifollicular papules**; maybe confused with psoriasis; eruptions spreads **cephalocaudally**.
- Clinically:
 - Areas of uninvolved skin, particularly on the trunk and limbs ('**islands of sparing**')
 - **Palmoplantar keratoderma**
 - **Keratodermic sandals** (orangish thickening of palms and soles).
- Treat with acitretin or isotretinoin.



Fig. 26.16: Keratodermic sandals

SEBORRHEIC DERMATITIS

- A misnomer! unrelated to seborrhea; maybe a/w yeast-like fungus, *Pityrosporum* (*Malassezia*) *orbiculare*.
- Chronic disorder characterized by **greasy scales** overlying erythematous patches or plaques in flexures, central areas of the face and scalp – ‘**stuck on**’ appearance.
- **MC site** is the **scalp**: recognized as **dandruff**.
- In infants, it may occur on the scalp (‘**cradle cap**’) or in the diaper area (‘**napkin dermatitis**’).
- Also maybe a/w **folliculitis**, marginal **blepharitis** and **erythroderma**.
- SD may be seen in patients with **Parkinson’s disease**, **HIV infection**, past history of **cerebrovascular accidents**.
- Treatment: Topical **glucocorticoids**; **shampoos** containing **coal tar** and/or **salicylic acid**.

ECZEMA (DERMATITIS)

- Dermatitis = ‘inflammation of the skin’; ‘Eczema’ = ‘a **boiling out**’ in Greek.
- Eczema and dermatitis are now used **synonymously**; called **dermatitis** in **USA**, and **Eczema** in **Europe**.
- Acute eczema: Exudation and cracking/scaling edema of the epidermis (**spongiosis**).
- Chronic Eczema: Thickening, **lichenification**, **fissures** and scratch marks; **pigmentation**, thickening of the epidermis (**acanthosis**).

- Eczemas are almost invariably **a/w itching**.
- Mainstay of treatment for all eczemas is **avoidance of irritants**; rest is as given in following table.

CONTACT DERMATITIS

Irritant Contact Dermatitis (ICD)	Allergic contact dermatitis (ACD)
Due to direct toxic effects of strong chemicals (Not immunological) - NO sensitization required - hence clinical manifestations occurs early <ul style="list-style-type: none">• Aka ‘Housewives’ eczema’, occupational dermatitis.• MC area of involvement are the hands.• Due to an inherent characteristic of a compound (Detergents, acids, alkalis) are common causes.	Due to immunological (delayed Type 4 hypersensitivity) - sensitization required and latent period is there before clinical features start <ul style="list-style-type: none">• In India parthenium - congress grass is MC cause of plant dermatitis (phyto-dermatitis) due to release of sesquiterpene lactane, SQL.
<ul style="list-style-type: none">• Strictly demarcated and often localized to areas where the irritant was occluded.• Napkin eczema in babies is common and due to irritant ammoniacal urine and feces.• Applying barrier creams prior to exposure to offending agent helps in ICD.	<ul style="list-style-type: none">• Nickel (MC metal) causing ACD (affects earlobes, wrists, back) due to nickel in jewelry, watches and bra clips.• ACD of the hand and wrists can occur due to rubber gloves.• Definitive diagnosis is by the patch test.

Patch Test

- **Confirmatory test** for ACD.
- **Occlusive patch** containing low concentrations of possible allergen placed in contact with the skin of upper back for **48 hours**.
- **Finn test**: Patch strips are small aluminium chambers containing the allergen.
- **TRUE test**: (Thin layer Rapid Use Epicutaneous test), Here pre-prepared patches are available.
- **Erythema and vesicles** at the site of patch = **positive test**
- **3 readings** are taken: At **48 hours** (immediately after patch removal); next at **day 4 (best reading time)** and at **day 7**.
- **Photopatch test**: used to detect chemicals which get activated by exposure to sunlight (photoallergens). Used for **parthenium** associated phyto-dermatitis.
- **Prick testing**: If **food or inhalant allergens** are suspected; after **10 minutes**, the sites are inspected for **wheel and flare** reactions.

Treatment of All Eczemas (including Contact Eczema)

Stage of eczema	Clinical features	Topical treatment of choice
Acute	Erythema, edema, vesicles, oozing	Moist compresses
Subacute	Crusting and scaling	Creams and moisturizers, emollients
Chronic	Lichenification	Ointments (with/without occlusion)

ATOPIC DERMATITIS

Age	Site of involvement
Infancy	Face, neck and extensor surfaces involved. Napkin area is frequently spared.
Childhood	Cubital fossa and popliteal fossae
Adults	The face, trunk and flexures.

- Atopic dermatitis is a/w
 - Allergy to **house dust mite allergens**.
 - Food intolerance
 - Food allergy
- Cardinal feature of atopic dermatitis is **pruritus** and scratching account for most of the signs.
- Family history of **Atopic Triad: Dermatitis, Asthma, and Allergic rhinitis**.
- **Hanifin and Rajka** diagnostic criteria are used for Atopic Dermatitis.



Fig. 26.17: Associations of atopic dermatitis

Clinical features of atopic dermatitis

- **Lichenification**: Thick, leathery skin due to constant scratching and rubbing with exaggeration of normal skin lines and hyperpigmentation.
- **Pityriasis alba**: Hypopigmented poorly demarcated areas on cheeks and extremities.
- **Ichthyosis**: Dry, scaly skin.
- **Keratosis pilaris**: Follicular openings are filled with horny plugs; small, rough bumps seen on the face, posterolateral arms, and anterior thighs.
- **Hyperlinear palms**: Increased number of skin creases on the palms.
- **Urticaria**: Hives (red, raised bumps), after exposure to allergen, or after exercise or a hot bath.
- **Cheilitis (perioral pallor)**: inflammation of the skin on and around the lips
- **Atopic pleat (Dennie-Morgan fold)**: An extra fold of skin that develops under the eye.
- **Hertoghe’s sign**: Thinning of the lateral half of the eyebrows.
- **Hyperpigmented lower eyelids**.
- Firm rubbing of the skin elicits ‘**white dermographism**’ with no erythema.

Treatment

- **Emollients** for dry skin; bathe only once daily.
- **Corticosteroid ointments** sparingly with tapering.
- **Tacrolimus** and **pimecrolimus** ointment (risk of **T cell lymphoma**, not useful in acute weeping lesions).
- in **50% cases**, disease **remits spontaneously** between 2 and 5 years; in adults it is milder.
- **Systemic therapy**: Oral prednisone, antihistamines, anti-staphylococcal antibiotic (**nasal mupirocin ointment**), phototherapy.
- In **recalcitrant cases**: Cyclosporine (calcineurin inhibitor), mycophenolate mofetil or azathioprine.



Fig. 26.18: Cubital fossae in atopic dermatitis

Special concerns in atopic dermatitis

- **Ocular Associations:** *Shield* cataract (*anterior subcapsular*) and *keratacanus*.
- **Genetic predisposition** (both parents affected >80% chances; one parent affected 50% chance of child getting affected).
- Serum levels of *IgE* are elevated.
- **Increased susceptibility** to *papilloma virus* (warts) and *molluscum contagiosum* and superinfection with *S. aureus*.
- Susceptibility to severe **HSV 1** infection – causing **Eczema herpeticum** or **Kaposi's varicelliform eruption**.

VARIOUS OTHER DERMATITIS

Pompholyx

- Pompholyx means 'bubble' in Greek; aka *dyshidrotic eczema*, *endogenous eczema*.
- It is often a/w *hyperhidrosis* (hence *dyshidrotic eczema*); *recurrent, itchy, vesicles or bullae affect the palms, sides of fingers (tapioca/sago grains like lesions) and soles*.
- May also occur in *nickel sensitive patients* after they ingest small amounts of nickel in food; a/w h/o *atopy*.
- Treat with topical and systemic *corticosteroids*.

Nummular (Discoid) Eczema

- MC seen on the limbs (*pretibial areas or dorsum of hands*) of elderly males.
- Multiple, 'coin-like', vesicular and crusted lesions are seen.

Lichen Simplex Chronicus

- Aka *circumscribed neurodermatitis*.
- Common in the *Indian subcontinent*.
- Predisposed areas are the *back of scalp/neck, medial aspect of ankle, extensor aspect of wrists or forearms and the genitalia*.
- Occurs due to an 'itch-scratch' cycle leading to dry leathery lichenified plaques.

Asteatotic Eczema

- Aka *xerotic eczema*, 'eczema craquelé' or 'winter itch'.
- MC on the lower legs of elderly during dry weather.
- It occurs as a 'crazy paving' pattern of fissuring on an erythematous background.

Stasis (Gravitational) Eczema

- Occurs on the lower legs and is often a/w signs of *venous insufficiency*.



Fig. 26.19: Pompholyx: vesicular lesions on the sides of the fingers

FIXED DRUG ERUPTION

- Fixed drug eruptions *recur in the exact same location* when the drug is repeated and *hyperpigmentation*, if present remains after healing.
- The eruption usually *appears within hours of administration* of the offending agent, and common locations include *erythematous plaques at the genitalia (glans penis): MC site; distal extremities, and perioral region*.
- Phenolphthalein, pyrazolone derivatives, tetracyclines, NSAIDs, *Sulfonamides* (TMP-SMZ), NSAIDs (ibuprofen, naproxen), allopurinol and barbiturates are major causes.
- **DRESS** (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome is characterized by the presence of *at least three* of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and *hepatitis* (Liver MC involved internal organ). Other systemic involvement includes *pneumonitis, myocarditis, pericarditis, nephritis, encephalitis and colitis*.



Fig. 26.20: Fixed drug eruption: circular lesions; bluish center with peripheral erythematous halo

HAIR BASICS

Hair Growth Phases

Anagen	<i>Hair Growth phase; vigorous mitotic activity occurs; melanogenesis occurs; 75–80% hairs are in anagen phase at any given time; determines ultimate length of hair</i>
Catagen	Next hairs enter this <i>Transitional (regressing)</i> phase; <i>club hairs</i> present; lasts for 2–3 weeks
Telogen	<i>Resting or degenerative</i> stage; lasts for 3 months

EXTRA EDGE

- The *highest density of hair follicles* is on the *scalp* between 500–1000/sq cm.
- It is normal to *lose about 50–100 scalp hair/day*.
- Hair follicles are found throughout the skin with the exception of *palms, soles and the genitalia* (glabrous skin).
- Human *scalp hair* grows about *1 cm/month* or *0.4 mm/day*.
- Hairs on the *scalp and beard* are examples of *terminal hairs*.
- *Eyebrows* have a *short anagen* phase and hence their length is limited.

ALOPECIA

Non-scarring alopecia

Primary skin disorder

- **Androgenetic alopecia** (MC type of alopecia)
- Telogen Effluvium
- **Alopecia areata** (exclamation mark hairs)
- Traumatic alopecia (trichotillomania, early traction alopecia)
- **Tinea capitis**

Systemic diseases

- SLE (*lupus hairs*)
- Secondary syphilis ('*moth eaten alopecia*')
- Hypo/Hyperthyroidism
- Hypopituitarism
- Deficiency of Protein, Biotin, Fe, Zn
- HIV infection

Drugs

- Warfarin, heparin, propylthiouracil, carbimazole, vitamin A, isotretinoin, acitretin, lithium, beta blockers, colchicine, and amphetamines

Scarring (cicatrizing) alopecia

Primary skin disorder

- **Lichen Planus**
- Folliculitis Decalvans
- Linear scleroderma (Morphea)
- Cutaneous lupus (chronic discoid lesions)
- Pseudopelade of Brocq

Systemic diseases

- Discoid lupus erythematosus
- Sarcoidosis
- Cutaneous metastasis
- Herpes zoster
- Bacterial and fungal infections

ALOPECIA AREATA (AA)

Pathophysiology

- *Recurrent, nonscarring alopecia* that can affect *any hair-bearing area*; autoimmune
- A/w *atopic* dermatitis, autoimmune disorders (hyper/hypothyroidism, vitiligo) and Down's.

Histology

- The germinative zones of the hair follicle are surrounded by *T lymphocytes (peribulbar lymphocytic infiltrate)*, which is described as a '*swarm of bees*'.

Presentation

- Most often *asymptomatic*, MC affects the *scalp*. *Well-circumscribed circular areas* of hair loss, 2–5 cm in diameter.
- During the active stage of hair loss, pathognomonic '*exclamation mark*' hairs are seen (broken off hairs of 3–4 mm long which taper off towards the scalp).
- **Ophiasis pattern** = hair loss on sides and the lower back of the scalp, **Sisapha pattern** = when hair loss spares the sides and back of the head.
- **Alopecia totalis** = 100% hair loss occurs on the scalp; **alopecia universalis** = complete loss of all body hair + scalp hair.
- *Sudden onset of alopecia totalis* can make a patient's hair '*go white overnight*' since often *gray/white hairs are spared*.
- **Nail involvement: Pitting is the MC finding**; may be a/w '*20 nail dystrophy*'.

Treatment

- **Intralesional corticosteroid** is the *treatment of choice* when < 50% scalp affected.
- Topical **minoxidil**, anthralin or tazarotene can be used.
- Topical **contact sensitizers**: DiPhenCyprone (DPC), DiNitroChloroBenzene (DNCB), squaric acid dibutyl ester (SADBE) can be used.

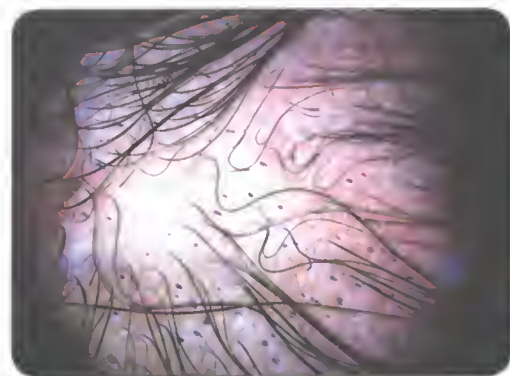


Fig. 26.21: Exclamation mark hairs



Fig. 26.22: Multiple patches of alopecia areata

Courtesy: Dr KT Ashique

ANDROGENETIC ALOPECIA (AGA)

- **MC type of alopecia; non scarring alopecia, physiological, affects men and women** (MC after menopause)
- Due to sensitivity of the affected hairs to the effects of **testosterone**.
- Presentation: **Miniaturization** of hairs along the midline of the scalp
- Male pattern AGA ('male-pattern' baldness)
 - **Frontal hairline recession** (First sign)
 - Loss of frontal and vertex hairs
 - Bitemporal recession and then
 - Crown involvement
 - Grading by **Hamilton Norwood** scale
- Female pattern AGA ('female-pattern' baldness)
 - NO loss of frontal hairline
 - Loss of midfrontal scalp hair—gradual increase of central parting (**christmas tree pattern**)
 - Diffuse thinning of the crown.
 - Grading by **Ludwig** staging
- Treatment:

- Topical **minoxidil** (both sexes)
- **Finasteride** (only in men) - 5-alpha reductase 2 inhibitor and **Dutasteride** (5-alpha reductase 1 and 2 inhibitor).
- **Spironolactone** (only in women)
- Hair transplants.

EFFLUVIUM

Telogen Effluvium

- A/w **stress** (**high fever, severe infection, malignancies, crash dieting, chronic iron deficiency**) or change in hormones (**postpartum**); large number of growing (anagen) hairs simultaneously enters the dying (telogen) phase.
- Telogen hairs are '**club**' shaped.
- **Non-scarring alopecia**, acute diffuse shedding of normal hairs **3-4 months after exposure to stressful agent**; reversible without treatment; reassurance required; hairs lost per day >150/day compared to normal of 70-100; on gently tugging the hair, large number of hairs with white bulbs come out.

Anagen Effluvium

- Increased daily anagen hair loss (normally hair are shed after telogen phase).
- Onset is rapid **within 2-3 weeks** after exposure to cause
- **Tapered fracture of hair shafts** is seen.
- Causes: **Radiation therapy** to head; nutritional (**severe PEM, Iron deficiency anemia**; Intoxications (mercury, boric acid, thallium, colchicine); drugs (**tamoxifen, doxorubicin**).

TRICHOTILLOMANIA

- **Impulse control disorder** with irresistible urge to pluck hair.
- **Varying lengths** of hair inside areas of hair loss (due to different force of pull on different days).
- Hair is NEVER completely lost in the patch; **non scarring alopecia**.
- **Orentreich/Friar-truck/tonsure sign**: Loss of central area (since easier to pull) compared to sparing of margins of the scalp.
- Histology: Pigmentation deposition in the follicle and **perifollicular hemorrhage**.
- Treatment: SSRIs, psychotherapy.

ACNE VULGARIS

- MC in **adolescents**, papulopustular **inflammatory** rash, MC on **face** and **trunk** maybe involved.

- Etiology: A combination of **androgen-dependence, overproduction of sebum, pilosebaceous duct hypercornification and blockage**, ductal colonization by **Propionibacterium acnes**.
- Main lesion—the **comedone** (**closed** = '**whitehead**' or **open** = '**blackhead**').
- In comedone, **linoleic acid is decreased, palmitic acid is increased; squalene peroxide** may cause increased inflammation.
- Healing, by **scarring** may occur.

Variants of acne

- **Acne conglobata**: Severe acne with oozing pus; MC in boys in tropical climates
- **Acne fulminans**: Nodulocystic acne, fever and joint pains
- **Acne venenata**: Occupational hazard in people exposed to oils/petroleum; also a/w vegetable oils used as cosmetics.
- **Acne 'excoriee de la jeune fille'**: Young girls with mild acne but **obsessional picking** scars the skin; may need systemic treatment.
- **SAPHO**: **S**ynovitis, **A**cne, **P**ustulosis, **H**yperostosis, **O**steitis
- **PAPA syndrome**: **A**D, **a**utoinflammatory; **P**yogenic arthritis, **P**oderma gangrenosum and **A**cne.
- **Resistant acne**: Suspect Polycystic ovary syndrome, androgen secreting tumor, XYY syndrome (tal male); congenital adrenal hyperplasia; Apert's syndrome (low IQ, acrocephalosyndactyly).

Treatment

- **Topical agents**: Salicylic acid (keratolytic), benzoyl peroxide, clindamycin, azelaic acid. (**Note: Azelaic acid** has also been used off label for **hyperpigmenting disorders like melasma and postinflammatory hyperpigmentation**).
- **Topical retinoids**: **Adapalene, tretinoin, tazarotene** (photoreactive—**best applied at bedtime**).
- Oral **antibiotics**: **Doxycycline, Minocycline or erythromycin**.
- **Severe nodulocystic acne**: **Treat with oral isotretinoin** (once daily dose for 5 months). **Side effects** include, **dry skin, cheilitis and hypertriglyceridemia, depression and teratogenicity; maximum dose is 2 mg/kg/day and maximum cumulative dose is 120-150 mg/kg**.
- **Hormones**: Antiandrogens—**Use in women only; Cyproterone acetate (DOC in PCOD associated acne will benefit hirsutism with contraceptive benefit also); spironolactone**.
- Cosmetic improvement of **scars by laser dermabrasion**.

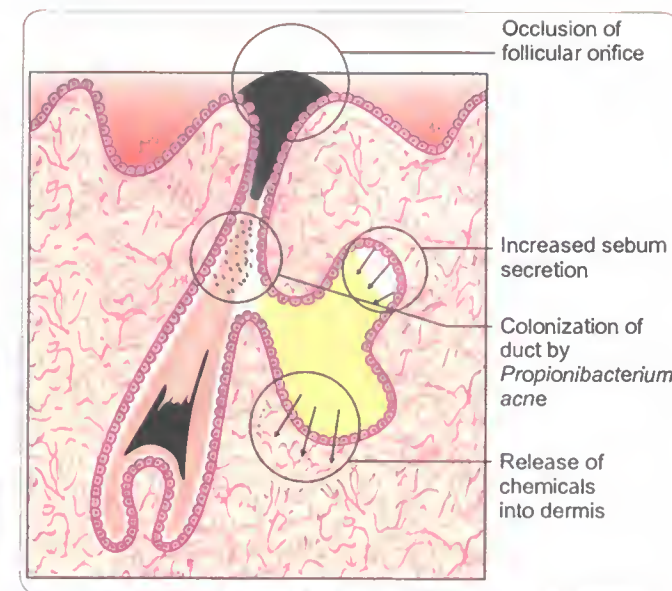


Fig. 26.23: Pathogenesis of acne

ACNE ROSACEA

- Inflammatory disorder affecting the **central face** (**cheeks, forehead and nose** in a typical cruciate pattern—**erythema, telangiectases and superficial pustules** but **NO comedones**).
- It affects **convexities of the face**—typically periocular and perioral areas are spared!
- **Seen in adults > 30 yrs**; seen MC in **women**, but **most severely affected are men**; **neurovascular component** (erythema and a tendency to flush easily).
- **Flushing of face** may be precipitated by hot drinks, alcohol, **heat/sun, emotion**.
- Rosacea of very long standing à connective tissue overgrowth, particularly of the nose (**rhinophyma - potato nose**).
- **Ocular problems**: **Keratitis with pannus**, blepharitis, iritis and recurrent chalazion.
- **Acne agminata**: Variant of **granulomatous rosacea**; also called **lupus miliaris disseminatus faciei** BUT NOT a/w TB.
- **Treatment**: **Oral tetracycline; topical metronidazole** are effective. **AVOID** fluorinated topical glucocorticoids (may actually elicit rosacea).

SKIN MANIFESTATIONS OF INTERNAL DISEASE

Erythema Nodosum

- **Lymphocytic vasculitis** in the deep dermis and subcutaneous fat, seen MC in **women**.

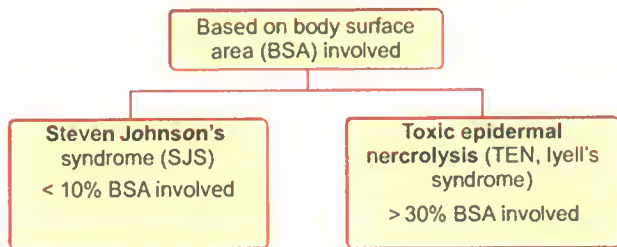
- Caused by:
 - **Infections:** Bacteria (***Streptococci MC***, TB, brucellosis, leprosy, yersinia), viruses, mycoplasma, rickettsia, chlamydia and fungi.
 - **Drugs:** Sulfonamides, oral contraceptives, dapsone.
 - **Systemic:** Sarcoidosis, ulcerative colitis, Crohn's disease, BCG vaccination.
- Presents as **Painful, palpable, dusky blue-red nodules**, MC on the **anterior shins**; malaise, fever and joint pains are common; the lesions *resolve slowly* over a month *leaving bruise-like marks* in their wake.
- Treatment: Bed rest and NSAIDs. Treat the underlying cause.

Erythema Multiforme (EM)

- Erythema multiforme **minor**: **HSV is MC** cause
- **Causes of EM:** **Herpes simplex**, Orf, mycoplasma infections; bacterial infections; **drugs** (sulfonamides, penicillin, barbiturates); **internal malignancy** or its treatment with radiotherapy.
- **EM minor:** 'Bull's eye' or 'target' or 'iris' lesions are seen; affects extensor surfaces, palms/soles and mucus membranes.

Erythema Multiforme Major

This term has been replaced by terminology as in flowchart here:



EXTRA EDGE

- 10–30% BSA involved = SJS/TEN overlap
- **Erythroderma:** Refers to **skin inflammation involving > 90%** of BSA.
- **Signs of EM major:** Hemorrhagic crusting of lips; affects the trunk more commonly than EM minor.

Pyoderma Gangrenosum

- **Unknown** etiology; a/w **inflammatory bowel disease (IBD)** — **Ulcerative Colitis (MC)** and Crohn's.
- **Deep ulceration with a violet border** that overhangs the ulcer bed, occur **MC on the legs**, also on **sites of**

trauma (pathergy); Peristomal PG (around stoma sites); **Pyostomatitis vegetans** (intraoral form occurring in patients with IBD).

- **Treatment:** Local wound care and dressings, treat systemic illness; surgery should be *avoided, if possible*, due to the **pathergic** phenomenon.



Fig.26.24: Pyoderma gangrenosum. Eroding ulcer on the leg with surrounding zone of erythema

OTHER ERYTHEMAS

Erythema marginatum	Rheumatic fever, Pink rings on trunk with serpiginous borders
Erythema chronicum migrans	Lyme disease (<i>Borrelia burgdorferi</i>), starts at site of tick bite
Erythema infectiosum (fifth disease)	Parvovirus B19 infection; Erythema of the cheeks ('slapped cheeks' appearance)
Erythema Annulare centrifugum	Drugs, Infections, Paraneoplastic
Erythema gyratum repens	Underlying malignancy; Numerous mobile concentric arcs and wavefronts that resemble the grain in wood
Erythema toxicum	Normal newborn term infants between the ages of 3 days and 2 weeks; disappears spontaneously
Erythema ab igne aka hot water bottle rash, fire stains, laptop thigh, granny's tartan and toasted skin syndrome	Skin reaction caused by chronic exposure to Infrared radiation in the form of heat

Contd...

Contd...

Erythema pernio	Exposure to cold
Erythema induratum	Bazin's disease (a/w tuberculosis); panniculitis on lower legs (calf) in women

SKIN MANIFESTATIONS OF DIABETES MELLITUS

- **Necrobiosis lipoidica diabetorum:** MC in IDDM, **yellowish-pink plaques**, on the lower legs/**ankles**.
- **Granuloma annulare:** **ring-like** papules and plaques; on the **dorsum of the hands and feet**.
- **Diabetic dermopathy** (Binkley's spots): Multiple, **brownish**, spots on the front of **shins**; more common in **males**.
- **Neuropathic ulceration:** Due to **Diabetic neuropathy** (on soles and feet).
- **Xanthoma:** Nodular deposits of **lipid within the histiocytes in the dermis**. **Touton giant cell** is seen.
- **Diabetic bullae:** Spontaneous appearance of **blisters on the extremities** (usually confined to **hands or feet**).
- **Skin thickening:** **Pebbling of the knuckles** to the diabetic hand syndrome.

SKIN MANIFESTATIONS OF INFECTIOUS DISEASES

Impetigo

	Impetigo contagiosa (Nonbullous impetigo)	Bullous impetigo
Etiology	Group A beta hemolytic streptococci more commonly; also <i>S. aureus</i>	Coagulase-positive group II <i>S. aureus</i> , most often phage type 71
Age	Preschool/young children	Neonates and infants
Clinical features	<ul style="list-style-type: none">• Thin-walled blisters on erythematous base. Rupture rapidly to leave honey colored crusts• Lesions spread without central clearing• Lymphadenopathy frequent• Scrum pox in rugby	<ul style="list-style-type: none">• Thick-walled persistent blisters on bland skin. Rupture only after a few days to leave thin varnish-like crusts• Lesions heal in center to form annular plaques• Lymphadenopathy rare
Sites affected	Face, especially around mouth and nose	Face and other parts of the body

Contd...

Contd...

	Impetigo contagiosa (Nonbullous impetigo)	Bullous Impetigo
Complications	<ul style="list-style-type: none">• Poststreptococcal glomerulonephritis, Ecthyma, scarlet fever, erysipelas, cellulitis, lymphangitis and, rarely, bacterial endocarditis	<ul style="list-style-type: none">• Staphylococcal scalded skin syndrome, pemphigus neonatorum, cellulitis, lymphangitis, pneumonitis, septic arthritis, osteomyelitis, and septicemia

Scarlet Fever

- **Caused by Group A beta hemolytic Streptococcus - Streptococcus pyogenes** (by pyrogenic exotoxins A, B, C; aka erythrogenic toxin)
- MC in children aged 2–10 years, usually follows group A streptococcal pharyngitis.
- Diffuse **blanchable erythema** beginning on face and spreading to trunk and extremities; **circumoral pallor**, 'sandpaper' texture to the skin, accentuation of linear erythema in skin folds (**Pastia's lines**); enanthem of white evolving into red 'strawberry' tongue; desquamation of palms and soles in second week.

Erysipelas

- Caused by **Group A beta hemolytic Streptococcus - Streptococcus pyogenes**.
- Recurrent erysipelas **secondary to lymphoedema** (*Staphylococcus aureus*); aka 'St Anthony's Fire'
- Bacterial inoculation into an area of **skin trauma** is the initial event; manifests as a **fiery-red, indurated, tense, shiny plaque**, with **raised, sharply demarcated advancing margins**.
- Lymphatic involvement is often manifested by overlying **skin streaking** and **regional lymphadenopathy**.
- **MC on the malar area of the face** and lower extremities.
- **Penicillin is the drug of choice**; other drugs - cephalexin, azithromycin.

EXTRA EDGE

- Erysipeloid is an **acute bacterial infection** of **traumatized skin** caused by **Erysipelothrix rhusiopathiae** (insidiosae); **direct contact** between meat or animals infected with *E. rhusiopathiae* and traumatized human skin results in erysipeloid.

Ecthyma Gangrenosum

- Skin manifestation of *Pseudomonas aeruginosa* bacteremia. EG usually occurs in critically ill, immunocompromised, neutropenic patients.
- Skin lesions of EG are characterized by hemorrhage, necrosis, surrounding erythema and histologic evidence of blood vessel invasion by bacteria; early lesion to a necrotic ulcer may progress within 12 hours; common in the gluteal or perineal region.
- Treatment: Antipseudomonal antibiotics.

Erythrasma

- Chronic superficial infection of the intertriginous areas of the skin caused by *Corynebacterium minutissimum* - normal human skin commensal.
- It is a *lipophilic, gram-positive, aerobic diphtheroid*.
- Wood's light examination: Shows coral red fluorescence of lesions secondary to the production of porphyrin by these diphtheroids.
- Well-demarcated, brown-red macular patches, wrinkled, with fine scales.
- Treatment: Antibiotics (erythromycin, clarithromycin).

VIRAL SKIN DISEASES

Herpes Zoster (HZ, Shingles)

- HZ is due to reactivation of the varicella-zoster virus (VZV) lying latent in the posterior root ganglion of a spinal nerve.
- If a patient without immunity to chickenpox contacts a patient with HZ, he may develop chickenpox.
- HZ mostly affects those past 50 years of age; HIV-infected patients are 20 times more likely to develop HZ.
- Clinically—unilateral vesicular eruption within a dermatome, often associated with severe pain; thoracic dermatomes are MC involved.
- Herpes zoster ophthalmicus (HZO): Hutchinson's sign: lesions on tip of nose, root and side of nose and inner corner of eye indicates ophthalmic branch of the trigeminal nerve involvement; HZO is a marker for stroke in the ensuing year.
- Herpes zoster oticus or Ramsay Hunt syndrome: Pain and vesicles appear in the external auditory canal, and there is loss of taste sensation in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved.

- Treatment: Oral aciclovir, famciclovir or valaciclovir for herpes zoster.
- Vaccine: A live attenuated VZV vaccine (19,400 pfu of Oka/Merck strain) of VZV; this vaccine should be offered to persons 60 years and older but CANNOT be used in children in place of varicella vaccine.

Postherpetic Neuralgia (PHN)

- Definition: Pain persisting even after 1 month of healing zoster (some consider 3 months).
- PHN is MC after involvement of the trigeminal region, in patients > 50 years.
- Early (< 72 hours after onset) antiviral treatment (famciclovir) of herpes zoster reduces the severity and duration of PHN.
- Treatment: Capsaicin cream or lidocaine patch; NSAIDs are ineffective; for persistent pain - oral amitriptyline, gabapentin or duloxetine may be used; if chronic pain regional blocks (stellate ganglion, epidural, infiltration), or peripheral nerve blocks may be used.

Herpes Simplex

- Herpes simplex virus (HSV) is a linear double stranded DNA virus.
- HSV-1 causes lesions of face and oropharynx. Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first episode HSV-1 infection while recurrent herpes labialis is the most frequent manifestation of reactivation HSV infection.
- Herpetic whitlow: HSV infection of the finger; occupational hazard in medicine and dentistry.
- Herpes genitalis: HSV infection of the genitalia, thorax and hands seen among wrestlers/contact sports.
- HSV-2 causes genital lesions (herpes genitalis).
- Treatment is with acyclovir or famciclovir.

Viral Warts

- Caused by human papilloma virus (HPV).
- Transmitted by direct skin contact; and for warts by sexual contact.
 - Common warts (verruca vulgaris) mainly by HPV 2.
 - Superficial plantar warts (mosaic warts) by HPV 2.
 - Deep plantar warts ('Mycetozoid warts') by HPV 1.
 - Plane warts (verruca plana) by HPV 3 and HPV 4.
 - Butcher's wart by HPV 7.
 - Anogenital warts (including condyloma acuminatum): by HPV 6 > HPV 11.

- The application of 3 to 5% acetic acid usually turns HPV-infected genital warts to a whitish color (aceto-whitening).
- Histopathology: Koilocytosis (vacuolation of superficial keratinocytes - ballooning degeneration).

Treatment of common warts

- First-line (Self administered by patient): Salicylic Acid (DOC for common warts); Trichloroacetic acid; Glutaraldehyde; Formalin; 5-FU
- Second-line (Done by physician): Cryotherapy (liquid Nitrogen); Electrocautery; Photodynamic therapy (PDT).
- Third line (Unresponsive cases): Intralesional injections (MMR, BCG, Candidal antigens); Interferon alpha; Oral Zinc. Oral retinoids; Intralesional bleomycin.

Treatment of genital warts

- Imiquimad: DOC (It stimulates toll like receptors TLR 7 and 8)
- Podophyllum resin
- Cryotherapy
- Surgery
- Interferon

EXTRA EDGE

- Epidermodysplasia verruciformis: It is a congenital condition with plane warts spread extensively on the arms, face, trunks, limbs and some lesions can transform to squamous cell carcinoma.
- Buschke-Lowenstein tumor, (verruca carcinoma): Solitary exophytic lesion that may destroy much of the penis, it is larger than condyloma acuminatum (hence giant condyloma). Locally invasive and recurrent but NO metastasis. Surgical excision required.



Fig. 26.25: Condyloma acuminatum: verrucous, fleshy plaque on glans. With permission

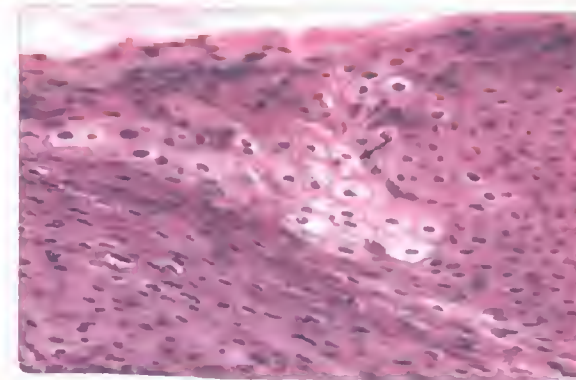


Fig. 26.26: Histopathology of warts—shows koilocytes which are epidermal cells with hyperchromatic irregular nuclei and a perinuclear halo

Molluscum Contagiosum

- MC and most prevalent type is MCV-1.
- Poxvirus infection characterized by multiple pearly, dome shaped, umbilicated flesh-colored or hypopigmented papules.
- Cytoplasmic inclusion bodies — Molluscum bodies.
- Common sites of involvement are the face, lower abdomen and genitals.
- Lesions are autoinoculable and spread by wet skin-to-skin contact.
- A/w AIDS and immunosuppression.
- Treatment is by curettage; applications of liquid nitrogen; Light electrosurgery with a fine needle.
- Topical cidofovir maybe effective.



Fig. 26.27: Molluscum contagiosum

Hand, Foot and Mouth Disease

- MC caused by Coxsackie virus A16; usually seen in infants and young children, highly infectious and spreads by direct contact; sore throat and red macules, vesicles and bullae may be seen on the mouth, hands and feet; lesions usually resolve in 1 week.

TUBERCULAR INFECTIONS OF SKIN

Lupus vulgaris

- **MC form of skin TB in India**
- Seen in previously infected/sensitized persons
- MC in **females**; often a/w **underlying active TB** in the lung or lymph nodes
- MC in **head and neck/buttocks**
- Present as **red-brown plaques**; that **heal at one end and progress at other end**; heals leaving **central scars**
- '**Apple-jelly nodules**' on **diascopy** (pressing lesion with glass slide)
- **Matchstick test positive**-If matchstick is pressed on lupus vulgaris lesion, it penetrates the thinned epidermis easily, but stands on itself without support on the firm dermal nodules.
- **Squamous Cell Ca** can develop within the plaques
- **Cartilage** (nose, ears) within the affected area is progressively destroyed (**lupus vorax**); **bone** usually is **spared**.

Scrofuloderma

- Skin TB that results from **direct extension from underlying tuberculous focus**, i.e. Infected lymph nodes, muscles or bones.

Tuberculous chancre

- Skin TB occurring in persons with **NO previous infection and immunity**; infection **follows an injury**, usually in children
- **Firm, NON-healing, shallow, NON-tender, undermined ulcer** with a granulomatous base a/w **painless regional lymphadenopathy**.

Tuberculosis verrucosa cutis (TVC)

- TVC occurs in **previously infected individuals** with a **high degree of immunity**, and may be from **infected sputum** or due to **handling infected material**
- MC seen on **hands and legs**; warty papule often mistaken for verruca vulgaris (**Anatomist's/postmortem/prosector's wart**); **NO regional lymphadenopathy**.

Tuberculids

- Tuberculids are **symmetric generalized exanthems** in the skin of tuberculous patients, possibly resulting from **hypersensitivity reactions** to tubercle bacillus. Typically, patients with tuberculids are in relatively good health and show (1) **Strongly positive Mantoux test**, (2) **Tuberculous involvement** (usually inactive) of viscera or lymph nodes, (3) **Absence of M. tuberculosis bacilli** in tissue by smear/culture and (4) **Satisfactory therapeutic response** of skin lesions to antitubercular treatment.
- Currently only 3 entities are accepted as tuberculids - **Papulonecrotic tuberculid**, **Lichen scrofulosorum**, **Erythema induratum** (Bazin's disease)

Swimming pool or fish-tank granuloma

- Caused by **M. marinum**; after contact with contaminated **tropical fish tanks, swimming pools or salt-water fish**; a small **violet nodule** or **pustule** may appear at a site of **minor trauma**; **lymphangitic spread** with several nodules up the extremity in a **sporotrichoid** fashion may occur; lesions often **heal spontaneously** (marine = water).

Buruli ulcer

- Caused by **Mycobacterium ulcerans**; chronic, necrotizing ulcer, painless and occurs **after penetrating skin trauma**; **spontaneously heal**, but frequently result in chronic **lymphoedema** and **disfiguring scarring**; Treat with **Excision** (Buruli Ulcer = M. ULcerans).



Fig. 26.28: Apple-jelly nodules are seen on diascopy

LEPROSY (HANSEN'S DISEASE)

About M. leprae (Micro+PSM)

- **Gerhard Armauer Hansen**, a **Norwegian** physician discovered the leprosy bacterium.
- **M. leprae** was the **first bacillus** to be **a/w a human disease**.
- **M. leprae** is an **obligate intracellular bacillus** that is confined to **humans, armadillos** in certain locales, and **sphagnum moss**.
- It is **acid-fast**, **indistinguishable microscopically from other mycobacteria**, and ideally detected in tissue sections by a **modified Fite stain**.
- **M. leprae** produces **NO known toxins** and is well adapted to penetrate and **reside within macrophages** yet it may **survive outside the body for months**.
- **M. leprae** grows best at **30 deg C** (less than human core body temp) - hence leprosy lesions localize to **cooler superficial body areas** (like earlobes, nose, testes, liver) and **superficial cooler nerves** (like ulnar, facial nerve).
- Can be cultivated **best** in **nine-banded armadillo** (*Dasypus novemcinctus*) - **Best for research purpose** also, cultivable in **foot pad of mice**, in **nude mice**, **SCID mice** and **Blebe mice**.
- **PGL-1** (Phenolic Glycolipid-1) present on the surface of bacillus and contributes to **pathogenesis**.
- **Doubling time** of leprosy bacilli is **11-13 days** (average **12 days**).
- Modes of **transmission**: droplets; contact to skin, breastmilk, transplacental, insect vectors, tattooing needles.

Classifications of Leprosy

Indian	Madrid	Ridley-Jopling
Indeterminate (I)	Indeterminate	Tuberculoid (TT)
Tuberculoid	Tuberculoid; at	Borderline
Borderline	raised Borderline	tuberculoid (BT)
Lepromatous Pure neuritic	Lepromatous	Borderline (BB)
		Borderline lepromatous (BL)
		Lepromatous (LL)

- The **Indian classification (clinico-bacterial)** is the official classification of Indian Leprosy Association (**Hind Kusht Nivaran Sangh**).
- Ridley-Jopling classification (immuno-histological) is based on 4 criteria
 1. Clinical
 2. Bacteriological (slit skin smear SSS)
 3. Histological (skin biopsy)
 4. Immunological criteria (lepromin testing)
- **MC type of leprosy in India** (as per latest published articles) is **Borderline Tuberculoid (BT)** (**Bharati**) (**BUT**, it's Tuberculoid leprosy, as per 19th Harrison, which says - '**In India and Africa, 90% of cases are tuberculoid; in Southeast Asia, 50% are tuberculoid and 50% lepromatous; and in Mexico, 90% are lepromatous**'. (If asked in exam, **Better choose BT > TT**).

Types of Leprosy

Indeterminate Leprosy

- An **early form** of leprosy where the immune system has not yet determined the appropriate response to the bacillus.
- Presents as **single, ill-defined, hypopigmented macule** on **cheeks, arms, thigh or buttocks**.
- **Sensation is normal** and **peripheral nerves are normal**.
- Histology shows **perineural lymphocytic infiltrate** (**NO granuloma**).
- **Bacteriologically negative** (**NO bacilli** are seen).
- **Spontaneous healing** may occur.

Tuberculoid Leprosy (TT)

- **Excellent cell mediated immunity** (lepromin test **positive**) and **bacillary load is low**.
- Histology: **Nodocaseating granuloma** with epithelioid and giant cells, **Grenz zone involved**
- One or a few sharply defined annular **asymmetric** macules or plaques with a tendency toward central clearing, **elevated well defined border**.
- Skin lesions **anesthetic early**.

Borderline Tuberculoid (BT)

- **SATellite lesions** and **Nerve Abscesses** are MC in **BT** leprosy (ulnar nerve abscess MC); ('**SANTA BanTa**').
- **BT** is MC type in India (**Bharati**)

Borderline Borderline (BB)

- **Many lesions** (8-10) that share features of both TT and LL.
- **Inner border** of lesions is **well defined** (like TT) and **outer border** is ill defined (like LL).
- **Most unstable** form of leprosy.

Borderline Lepromatous (BL)

- **Numerous small lesions (uncountable)** - all kinds of **bizarre lesions** in single patient distributed asymmetrically.
- **Inverted Saucers shaped** lesions are seen.
- **Perineural fibroblast proliferation** forming an '**onion skin**' in cross section.

Lepromatous Leprosy

- **Decreased cell mediated immunity** (CMI) and **bacillary load is increased** (lepromin test **negative**).
- **Perfectly symmetrical** lesions; earliest sign is **nasal stuffiness and epistaxis**.
- Histology shows **clear subepidermal free (grenz) zone**, **foamy macrophages** laden with acid-fast bacilli (**Virchow or Lepra cells**), and many intracellular bacilli, frequently in spheroidal masses (**globi**). **Clear Grenz zone present**. Epithelioid cells and giant cells (**granuloma**) are **NOT** found.
- **Dermatofibroma** papules; **leonine facies** and **eyebrow alopecia**.
- **Hypoesthesia** a late sign.
- **M. leprae PGL-1 antibodies** present in 95% cases.

Pure Neuritic Leprosy

- Only nerve involvement and **NO skin lesions**; bacteriologically **negative**.

EXTRA EDGE

As the patient moves **from TT to LL** type please note that

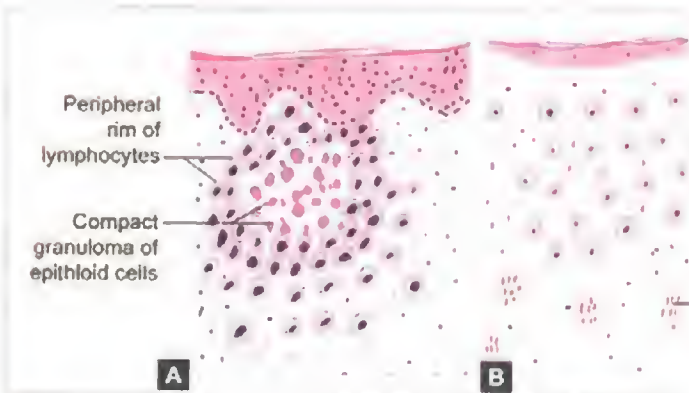
- Granuloma size decreases
- Foams cells, Grenz zone, Bacillary load increases
- Number of lesions increases
- Well-defined elevated margins becomes ill-defined
- Large lesions become smaller and more numerous

Other leprosy subtypes

- Histoid Leprosy**
- A type of LL usually a/w **dapsone resistance**.
 - Was more common earlier when only dapsone was given for treatment.
 - Shiny papules and nodules with intervening normal skin.
- Lucio Leprosy**
- A type of **non-nodular LL**, more common in Mexico and Central America.
 - A/w **diffuse infiltration** of skin - hence *no wrinkles and a shiny face* is seen (hence '**lepra bonita**' - 'pretty leprosy!')
 - **Lucio phenomenon**: characterized by **arteritis** and **ulcers on legs**, is limited to patients with diffuse lepromatous disease and **Lazorine** leprosy; exclusive to patients of Mexico and Caribbean.



Fig. 26.29: Lepromatous leprosy: infiltrated skin thrown into folds giving leonine facies



Figs 26.31A and B: Diagrammatic representation. A. Tuberculoid leprosy; B. Lepromatous

Nerve Involvement

- Target organ = nerves.
- Earliest sensation lost is **temperature**.
- MC peripheral nerves
- **100%** patients
- MC nerve taken
- MC cranial nerve is 1st to be affected

Fig. 26.30: Lepromatous leprosy: healed with gross mutilation, including depressed nose

Other leprosy subtypes

- Histoid Leprosy**
- A type of LL usually a/w **dapsone resistance**.
 - Was more common earlier when only dapsone was given for treatment.
 - Shiny papules and nodules with intervening normal skin.
- Lucio Leprosy**
- A type of **non-nodular LL**, more common in Mexico and Central America.
 - A/w **diffuse infiltration** of skin - hence *no wrinkles and a shiny face* is seen (hence '**lepra bonita**' - 'pretty leprosy!')
 - **Lucio phenomenon**: characterized by **arteritis** and **ulcers on legs**, is limited to patients with diffuse lepromatous disease and **Lazorine** leprosy; exclusive to patients of Mexico and Caribbean.



Other involvement in leprosy

- **Other organs involved** in leprosy = **eyes, kidneys, testes**.
- Organs **NOT** involved: CNS, female reproductive system; Lungs, prostate, breasts.
- Eyes: Iritis with iris microgranulomas (**iris pearls**), **corneal beading** and **Facial N** involvement can cause **lagophthalmos**, **exposure keratopathy**.
- Kidneys: **Secondary amyloidosis** is MC (especially in LL); In glomerulonephritis, **Mesangiolipomatosis** is MC.

Leprosy Reactions

Leprosy reaction	Type 1 reaction (reversal/upgrading reaction)	Type 2 (Erythema Nodosum Leprosum, ENL)
Mechanism	Cell mediated (type 4) hypersensitivity (1 + 4 = 5)	Immune complexes, Arthus phenomenon (type 3 hypersensitivity) (2 + 3 = 5)
Seen in	In the borderline	LL > BL patients, most

Sure Success MAGIC



Fig. 26.30: Lepromatous leprosy: healed with gross mutilation, including depressed nose

Nerve Involvement in Leprosy

- Target organ of *M. leprae* is **Schwann cell** of peripheral nerves.
- Earliest sensation lost in leprosy is **thermal sensation/temperature**.

- The reactions are of two types: **Early Fernandez** reaction (read at **48 hours**); **Late Mitsuda** reaction (read at **21 days**).
- The **early reaction** is induced by the **soluble constituents** of the leprosy bacilli and the **late reaction** by the **bacillary component** of the antigen.
- It is a useful tool in evaluating the **immune status (CMI)** of leprosy patients.
- Leprosin test is **NOT** a diagnostic test. It is unique among all tests for CMI in that it not only measures pre-existing CMI, but is in fact a **mini-dose vaccine**.
- It is of great value in **estimating prognosis** in leprosy of all types.

Slit Skin Smear (SSS)

- Slits are made on the skin with a blade and stained for AFB (4 sites as per WHO, but minimum 3 sites - **one earlobe** and **two active lesions**).
- On AFB staining 3 patterns may be seen
 - **Solid (S)** bacilli = viable bacilli

Other involvement in leprosy

- **Other organs involved** in leprosy = **eyes, kidneys, testes**.
- Organs **NOT** involved: CNS, female reproductive system; Lungs, prostate, breasts.
- Eyes: Iritis with iris microgranulomas (**iris pearls**), **corneal beading** and **Facial N** involvement can cause **lagophthalmos**, **exposure keratopathy**.
- Kidneys: **Secondary amyloidosis** is MC (especially in LL); In glomerulonephritis, **Mesangiolipomatosis** is MC.

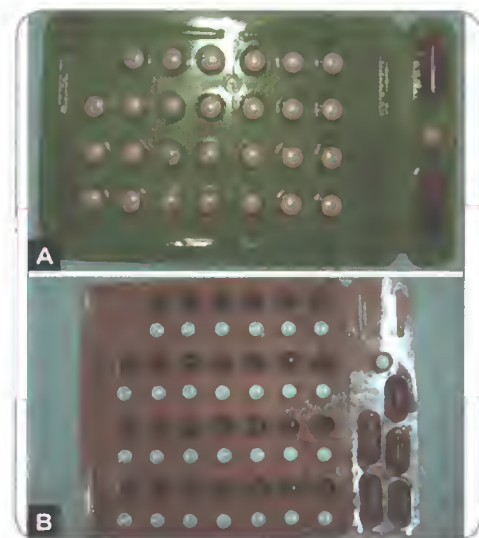
Leprosy Reactions

Leprosy reaction	Type 1 reaction (reversal/upgrading reaction)	Type 2 (Erythema Nodosum Leprosum, ENL)
Mechanism	Cell mediated (type 4) hypersensitivity (1 + 4 = 5)	Immune complexes, Arthus phenomenon (type 3 hypersensitivity) (2 + 3 = 5)
Seen in	In the borderline spectrum, BT > BB , BL patients (most severe in BL)	LL > BL patients, often in the late of the initial year of treatment
Clinical features	Painful tender nerves. Loss of function Inflammation (swollen and erythematous) of existing skin lesions NO fever Other organs not affected	New tender , in subcutaneous on face and legs; ulcerate; Arthralgia , uveitis , neuritis , lymphadenitis , glomerulonephritis , hepatitis , Fever

Multibacillary (MB) leprosy		
Supervised	Daily	Duration
600 mg Rifampicin + 100 mg Dapsone + 300 mg Clafazimine	100 mg Dapsone + 50 mg clofazimine	For 12 months (to be finished within 18 months)

EXTRA EDGE

- Earlier surveillance periods (after completion of treatment) for **PB** cases was for **2 years** and **MB** cases was for **5 years**; BUT **NOT required now** after MDT as per WHO.
- Treatment of **single skin lesion paucibacillary leprosy** is **ROM** – a **single dose** of Rifampicin, Ofloxacin and Minocycline - NO longer used in India since it has more failure rates.
- Mnemonic: For **PB** = **D/R** and for **MB** = **DC/DCR** where numerator is daily and denominator is monthly treatment.
- **Newer drugs (second line)** used in leprosy treatment are
 - Ofloxacin, Pefloxacin (most bactericidal among II line drugs)
 - Minocycline
 - Clarithromycin.
- **Most effective bactericidal drug** against *M. leprae* is **Rifampicin**.
- **MDT** (multi drug therapy) is NOT contraindicated in HIV infected persons and is safe in pregnancy.
- **Defaulter** is a leprosy patient on MDt who has not collected treatment for **12 consecutive months**.
- Side effect of clofazimine:
 - Hyperpigmentation of skin
 - Discoloration of body secretions
 - Ichthyosis
- **Dapsone syndrome** (5th week syndrome) = Erythroderma + fever + lymphadenopathy + hepatitis 5 weeks after taking dapsone.



More Important Points in Leprosy

- **Downgrading reaction**, which clinically minor reversal reactions, are common in untreated patients and in women during the third trimester of pregnancy.
- The **histamine test** is a very **reliable** method for detecting at an early stage, **peripheral nerve damage** due to leprosy. If nerve supply is destroyed due to leprosy, the response is lost.
- **Chaulmoogra oil** is a plant compound that was developed in Burma (now Myanmar) in the early 1900s. It was found to have weak antileprous properties and was the **first effective treatment** for leprosy.
- Nerve biopsy in leprosy is usually taken from **Sural nerve**.

XERODERMA PIGMENTOSUM (XP)

- AR; defect in **nucleotide excision repair** leading to **deficient repair of DNA damaged by ultraviolet radiation (sun-exposure)**; there is abnormal response of **poly (ADP-ribose) polymerase** to UV light exposure.
- The skin is **normal at birth**; XP is characterized by **photosensitivity, pigmentary changes, premature skin aging and development of malignant tumors** (SCC, BCC, etc.) in **sun-exposed areas** of the body.
- **Ocular problems** (seen in 80%): consist of **dry eye, photophobia, symblepharon, corneal ulceration**.
- **De Sanctis-Cacchione syndrome** = XP + **neurological abnormalities** (mental retardation and cerebellar ataxia), **hypogonadism and dwarfism**.
- Antenatal diagnosis is possible by amniocentesis or chorionic villi sampling. **Unscheduled DNA synthesis** is the classic method for diagnosis. A faster technique is the **alkaline comet assay** (single cell gel electrophoresis assay).
- **Treatment: Sunscreens; Oral retinoids** (side effect: **irreversible calcification of ligaments and tendons**).
- Xeroderma patients **cannot repair 'pyrimidine dimers'** formed by UV light damage in the skin.

MYCOSIS FUNGOIDES (CUTANEOUS T CELL LYMPHOMA)

- **Non-Hodgkin's** type lymphoma presenting with skin infiltration; MC of **T cell origin**; MC in **middle aged**.
- **Mycosis fungoides**
 - **Pruritic localized erythematous plaques** on the **trunk** > 5 cm in diameter!; patients maybe treated for decades before actual diagnosis!
 - Histology shows pleomorphic lymphocytes in clusters within the epidermis called **Pautrier's microabscesses**.

Figs 26.32A and B: Multidrug therapy of leprosy: WHO supplied blister packs: A. For paucibacillary leprosy (adult); B. For multibacillary leprosy (adult)

- **Sezary syndrome**
 - Advanced mycosis fungoides with **lymphadenopathy** and **visceral spread**
 - Generalized exfoliative erythroderma, and circulating **atypical T lymphocytes (Sezary cells)** are seen (by T cell gene rearrangement test)
 - Eosinophilia maybe seen.
 - **Dermatopathic lymphadenopathy** is present in 75% cases.
- **Treatment:**

Localized disease

- Topical corticosteroids
- Topical nitrogen mustard
- **Bexarotene** gel
- PUVA

For advanced disease

- PUVA + oral retinoids
- **Electron beam** therapy
- **Interferon** alpha
- **IL-12** and **Denileukin**
- **Histone deacetylase inhibitors, HDAC:** Romidepsin and vorinostat (second line therapy for CTCL (in patients with failed prior systemic therapy)
- **Extracorporeal photopheresis** (First line for sezary cells in blood)
- **Alemtuzumab** (anti-CD52 IgG antibody)

URTICARIA

- **Urticaria ('hives')** are itchy red papules that arise suddenly, often within a few minutes and last transiently (6–24 hours).
- **Allergic (type 1) hypersensitivity** due to **histamine release** from mast cells in the skin. Sun-exposure (**solar urticaria**), cold, pressure (**cold urticaria**), after hot baths, spicy food, hot food, exercise and sweating (**cholinergic urticaria**). Drug induced urticaria (**common** with **ACE inhibitors, penicillin, aspirin** and blood products and any drug).
- **Dermatographic urticaria** (**dermatographism** or 'skin writing') is the **MC physical urticaria**, in which the skin becomes raised and inflamed when stroked, scratched, rubbed, and sometimes even slapped. Exaggeration of the normal '**triple response**'.

ANGIOEDEMA (QUINCKE'S DISEASE)

- Angioedema is involvement of deeper subcutaneous tissue with **non-pitting edema** of the face (lips, eyelids), palms, soles, and genitalia.

- **Laryngeal edema and hypotension can lead to life-threatening difficulties in swallowing and breathing.**
- Inciting factors: eating **peanuts**, ACE inhibitor and angiotensin receptor blocker therapy.
- Remove aggravating factor; **H1 Antihistamines**, for acute angioedema; IV **glucocorticoids**.
- For **bradykinin mediated hereditary angioedema** (including that caused by **ACE inhibitors**) - **ecallantide** (plasma kallikrein inhibitor) and **icatibant** (bradykinin beta-2 receptor antagonist) are FDA approved.

Acrodermatitis Enteropathica

- **AR; malabsorption of dietary zinc** occurs; symptoms occur within the first few months after birth (esp. after discontinuation of breastfeeding).
- Symptoms are **periorificial** (mouth, anus) and **acral dermatitis, alopecia, intractable diarrhea, bizarre neurologic symptoms, variable combined immunodeficiency, impaired wound healing** and an often-fatal outcome. Rapid improvement occurs when treated with IV or oral zinc. **Lifelong Zn** supplementation required.
- Oral dosage = in children 0.5-1.0 mg/kg/day of elemental zinc; **Zinc sulfate** 4.4 mg = 1 mg elemental zinc; (i.e. 220 mg = 50 mg)

LUPUS ERYTHEMATOSUS

Acute Cutaneous LE

- **Erythema** of the nose and **malar eminences** in a '**butterfly**' distribution. It is **photosensitive, non-scarring, and telangiectases** may develop.

Discoid LE (DLE)

- Discrete lesions most often on the **face, scalp or external ears**; **erythematous papules or plaques** with a **thick, adherent scale** that occludes hair follicles (**follicular plugging**); when the scale is removed, its underside will show small excrescences that correlate with the openings of hair follicles and is termed a '**carpet-tack/ thumbtack**' appearance; long-standing lesions develop **central atrophy, scarring and hypopigmentation**.
- Treatment for both: **sun-protection, corticosteroids** (topical or intralesional) and **antimalarials** (**hydroxy-chloroquine, chloroquine, quinacrine**).

DERMATOMYOSITIS (DRM)

- DRM is usually a/w **polymyositis** as a symptom complex; bilateral **proximal muscle** weakness.
- About 25% of patients with DRM have **internal malignancy (MC ovarian Ca)**.

- '**Antisynthetase syndrome**' = polymyositis and DRM + inflammatory arthritis, fever, Raynaud phenomenon, '**mechanic's hands**' (hyperkeratosis along the radial and palmar aspects of the fingers) **interstitial lung disease**, and often severe muscle disease a/w **anti-Jo1**, **anti-PL7/PL12** antibodies.

Signs of dermatomyositis

- ▶ **Heliotrope rash**: Purple red discoloration of upper eyelids - MC manifestation.
- ▶ **Gottro's papules**: Violaceous flat-topped papules over bony prominences of hands, particularly the **MCP** joints and **PIP** joints.
- ▶ **Dowling's lines**: Linear erythematous squamous lesions on the dorsal surface of the fingers over the metacarpals.
- ▶ **Poikiloderma** may occur on exposed skin such as the extensor surfaces of the arm, the 'V' of the neck or the upper back (**Shawl sign**).
- ▶ **Poikiloderma** (short for *Poikiloderma vasculare atrophicum*) consist of mottled hypo/hyperpigmentation (poikilo), telangiectasias (vasculare) and progressive atrophy of the skin (atrophicum).
- Lab diagnosis: elevated **creatine kinase** and **ANA**; **anti-Mi-2** a/w **amyopathic DRM**; **anti-155/140** a/w **DRM with malignancy**.
- **Best diagnostic test is Muscle Biopsy**; In DRM - **pathognomonic** is **perifascicular atrophy** (around muscle fascicles, whereas, in polymyositis endomysial infiltration of the inflammatory infiltrate is present).
- **Treatment**: Corticosteroids; immunosuppressives; sunscreens, antimalarial agents and/or methotrexate.

ICHTHYOSIS

- **Ichthyosis vulgaris**: **AD**, **MC** and **develops around puberty** as scaly lesions on the extensor surfaces of extremities (sparing the flexures); palms and soles are involved; mild dry skin with follicular accentuation (**keratosis pilaris**).
- **Sex-linked ichthyosis**: **XLR**, begins **shortly after birth**; the generalized scaling is more severe and affects extensor as well as flexor surfaces but palms and soles are **spared**; a/w cryptorchidism, testicular cancer and cataract/corneal opacities; due to **deficiency of steroid sulfatase**; a/w history of postmature pregnancies and difficult labor.
- Histology: **hyperkeratosis**.
- **Treatment**: Topical **emollients** and **keratolytic preparations** (salicylic acid); topical tretinoin may be used, oral retinoids (acutretin, isotretinoin).

Ichthyosis presenting in neonatal period

- ▶ **Congenital Ichthyosiform Erythroderma (CIE)**: Neonatal may appear diffusely red with a fine, white scale.
- ▶ **Epidermolytic hyperkeratosis**: Presents with widespread denuded areas and bullae - hence its older name **bullous CIE**; the hyperkeratotic component develops later.
- ▶ **Collodion baby**: Baby is born covered by a shiny transparent membrane, which gradually peels off after a week or so, the peel looking like 'collodion' (a gluey solution of nitrated cotton in alcohol and ether used in surgery and photography).
- ▶ **Harlequin fetus**: Baby is born encased in thick abnormal fissured, hyperkeratotic skin and is a/w rudimentary ears, ectropion and eclabium. Child rarely survives beyond the first week.



Fig. 26.33: A case of classical ichthyosis vulgaris: Characteristic scaling on trunk

Courtesy: Dr Santanu Banerjee, Dr Resham

INCONTINENTIA PIGMENTI

- Aka (**Bloch-Sulzberger's dis**)
- **X-linked Dominant**; affects **skin, eyes and CNS**.
- **On Histology**: **Stage 3**: free melanin or in macrophages in the dermis - led to the term 'incontinence of pigment'
- **Skin**: Hyperpigmented streaks and whorls which **respect Blaschko's lines**, occur mainly on trunk and fade in adolescence. Lasts from 6 to 14 years.
- **Ocular changes**: seen in 30% of patients and asymmetric; diffuse **mottled hyperpigmentation of retina** (**pathognomonic**); also consistent finding is abnormalities of peripheral retinal vessels with areas of non-perfusion in the outer retina.
- **Hair**: Alopecia (scarring), wooly hair (lusterless, wavy, coarse).
- **Nail changes**: Ridging, steaking or pitting; brittle nails, onychogryphosis.

- **Teeth** (dental) changes: Seen in two-third of patients; **Hypodontia**, **microdontia**, **peg-shaped teeth**, **delayed eruption**, **malpositioning and impaction**; Enamel and tooth strength are **NORMAL**; **Neurological**: **Seizures and mental retardation**, BUT majority are normal.

MORE SKIN CONDITIONS

- Caused by **hookworm** (nematodes) *Ankylostoma braziliense* (MC), *A. caninum*, *Necator americanus*, *Strongyloides stercoralis* ('larva currens'), *Gnathostoma*, *gasterophilus*.
- It presents as an **erythematous, serpiginous, pruritic** cutaneous eruption caused by **percutaneous penetration** and subsequent **migration of larvae**.
- The **treatment of choice** is **topical thiabendazole**; oral ivermectin, albendazole may be used in rare cases.

Skin manifestations of primary amyloidosis

- ▶ **MC skin lesions are petechiae or ecchymoses**
- ▶ '**Pinch purpura**' = **purpura** on pinching the skin
- ▶ '**Post-proctoscopic purpura**': Spontaneous purpura around the eyes or is seen following proctoscopy or vomiting.
- ▶ **Lichen amyloidosis/papular amyloidosis** is the **MC form of localized cutaneous amyloidosis**. Pruritic, flesh-colored to brown papules MC on shins.
- ▶ In **macular amyloidosis**, pruritic macular hyperpigmentation occurs MC in the interscapular area.

Polymorphous Light Eruption (PLE)

- A positive **family history** of **sunlight sensitivity**; sun exposure causes erythematous macules, papules, and bullae often in a **photodistribution** (face and neck, chest, and dorsal arms and hands). MC with **UVA** light.
- Sometimes gradual **improvement** with continuing sun exposure occurs (aka '**hardening**').
- PLE in Native (north and south) Americans with a positive family history is called '**actinic prurigo**'.
- Treatment: Mainly **sunscreens**; topical steroids, beta-carotene, antimalarials and PUVA.

Fitzpatrick skin type classification

- ▶ Type I-Always burns, never tans (freckled skin)
- ▶ Type II-Usually burns, tans with difficulty (blonde hair, blue eyes)
- ▶ Type III-Sometimes mild burn, gradually tans (very common)
- ▶ Type IV-rarely burns, tans with ease (Mediterranean caucasian skin)
- ▶ Type V-Very rarely burns, tans very easily (dark brown, mid-eastern skin type)
- ▶ Type VI-Never burns, tans very easily (black)

Sweet's Syndrome

- Aka (**Acute Febrile Neutrophilic Dermatitis**)
- **Yersinia** infection; Malignancy (10% cases - **MC AML**; Solid tumors (of genitourinary tract); Drugs (**all-trans-retinoic acid**, granulocyte stimulating factors). Idiopathic (MC in women following respiratory tract infection).
- Affects **F>M**
- **Red to red-brown plaques and nodules**, painful and occur on the **head, neck, and upper extremities**.
- Also **fever, neutrophilia, and a dense dermal infiltrate of neutrophils** in the lesions.
- Extracutaneous sites of involvement = joints, muscles, eye, kidney (proteinuria, occasionally glomerulonephritis), and lung (neutrophilic infiltrates).
- **Reddish-orange perifollicular papules**; maybe confused with psoriasis; eruptions spread **cephalocaudally**.
- Areas of uninvolved skin, particularly on the trunk and limbs ('**islands of sparing**'); **palmoplantar keratoderma**; **keratodermic sandals** (orangish thickening of palms and soles).
- Treat with **acitretin** or **isotretinoin**.

HYPOPIGMENTATION

- **Oculocutaneous albinism (OCA)**
 - ▶ **AR**; mutations in **tyrosinase gene** (type 1, type 1A - total **absence of tyrosinase**) or **P gene** (type 2); pale/pinkish complexion with yellowish hair and blue/pink eyes; **nystagmus**, **photophobia**; severe **refractive errors**; extremely sensitive to solar UV rays and often develop **skin cancer**. Albinos are unable to synthesize melanin. Use sunscreens for UV protection.
- **Hermansky Pudlak syndrome**
 - ▶ **AR**, **OCA** (tyrosinase positive, meaning can develop some pigmentation—partial albinism), bleeding from **platelet dysfunction**, **granulomatous colitis**, cardiomyopathy and **interstitial lung disease**.
- **Chediak-Higashi syndrome**
 - ▶ **AR**, **OCA**, **nystagmus**, **peripheral neuropathy**, and **mental retardation** in some, and **phagocyte dysfunction** leading to repeated *S. aureus* pyogenic infections.

Vitiligo

- ▶ MC is **vitiligo vulgaris**.
- ▶ **Bilateral, symmetrical** white patches (due to **absence of epidermal melanocytes**) sometimes with a **hyperpigmented border and scalloped margins**; **leucotrichia** (depigmented hair) is a poor prognostic factor.
- ▶ Associations: **autoimmune disorders** (**thyroid disorders** MC, diabetes mellitus, alopecia areata, Addison's disease, hypoparathyroidism, premature ovarian failure).
- ▶ Treat by **PUVA** and camouflage cosmetics.

• Piebaldism

- **AD, white forelock** and **symmetrical white hypopigmented macules**; islands of normal pigmentation maybe seen; a/w **KIT gene mutation**.
- **Waardenburg syndrome** = Piebaldism + **sensorineural deafness, dystopia canthorum, heterochromia irides** and early graying.
- **Shah-Waardenburg syndrome** = Waardenburg synd + **Hirschsprung disease; AD or AR**.
- **VKH syn** (Vogt-Koyanagi-Harada)
 - **Vitiligo, poliosis** (circumscribed loss of pigments in hair), **uveitis, aseptic meningitis** and **tinnitus** with hearing loss.
- **Chemical leucoderma (acquired vitiligo)**
 - Contact vitiligo due to **Bindis and footwear straps** are due to chemicals containing **para tertiary butyl-phenol**.

EXTRA EDGE

- **Pigment dilution disorders** = disorders a/w **hypopigmentation** – includes all above disorders plus **Menke's kinky hair syndrome; Phenylketanuria; Hamacystinuria**; Tuberous sclerosis; Incontinentia pigmenti; Ataxia telangiectasia.
- **Nevus Anemicus**: Is a sporadic, congenital, persistent, pale patch developing secondary to vasoconstriction.
- **Nevus Achromicus (depigmentasus)**: A single well-defined hypopigmented patch; on **diascopy** (pressing with glass slide), the lesion border is not lost and the lesion does NOT merge into the surrounding skin (unlike *nevus anemicus*).
- In **albinism** - normal melanocytes BUT absent melanin production; In **piebaldism** - NO melanocytes and NO melanin.

HYPERPIGMENTATION

Café au lait spots

- Seen in **neurofibromatosis** (smooth 'coast of California' appearance) and in **McCune Albright syndrome** (irregular 'coast of Maine' appearance)
- **Café Au Lait Macules** also seen in: Pulmonary stenosis (Watson syndrome); Tuberous sclerosis; LEOPARD syndrome; Multiple endocrine neoplasia (MEN); Few normals.

Hyperpigmentation syndromes with acronyms

- **LAMB**, Lentigines, Atrial myxomas, Mucocutaneous myxomas, and Blue nevī
- **LEOPARD**, Lentigines, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis and subaortic valvular stenosis, Abnormal genitalia, Retardation of growth, and Deafness (sensorineural)
- **NAME**, Nevi, Atrial myxoma, Myxoid neurofibroma, and Ephelides (freckles)
- **POEMS**, Polyneuropathy, Organomegaly, Endocrinopathies, M-protein, and Skin changes
- **Carney complex** is another name for LAMB and NAME syndromes.

Contd...

Nevus

- **Nevus of Ota** is a hamartoma of dermal melanocytes. Clinically, it presents as a blue/gray patch on the face within the distribution of the **ophthalmic and maxillary branches of the trigeminal nerve**; maybe uni/bilateral and, may also involve **ocular** (conjunctiva, iris, retina) and **oral mucosal** surfaces.
- **Nevus of Ito**, is a dermal melanocytic hamartoma affecting the **shoulder area**; it often occurs in a/w nevus of Ota in the same patient but is much less common.
- **Becker nevus**: Starts as a **brown patch**, MC over the **shoulder, upper chest, or back**; pigmentation commonly occurs in the **peripubertal period** and the patch expands during the first several years; several months to years after the appearance of pigmentation, thick **brown-to-black hairs develop both within the patch** and **acne vulgaris** may develop.

Diffuse hyperpigmentation

- Endocrinopathies: **Addison's disease, Nelson syndrome**, Ectopic ACTH syndrome, Hyperthyroidism
- Metabolic: Porphyria cutanea tarda, hemochromatosis, vitamin B12, folate deficiency, pellagra, malabsorption, including Whipple's disease
- Metastatic melanoma
- Autoimmune: Biliary cirrhosis, scleroderma, POEMS syndrome, Eosinophilia-myalgia syndrome
- **Drugs and metals** (e.g. arsenic, busulfan, minocycline, hydroxychloroquine, bleomycin, cyclophosphamide, 5-FU)

EXTRA EDGE

- **Chlaasma (melasma)**: MC in **females** on the **bridge of the nose** and **cheeks**; acquired hypermelanosis **exacerbated by sun exposure, pregnancy, OCPs** and **antiepilepsy** drugs.



Fig. 26.34: Becker's nevus on the left shoulder and back

Courtesy: Dr Santanu Banerjee

NAILS AND DISEASE

- **Onycholysis**: (Destruction of nails) seen with **hyperthyroidism, fungal nail infection, psoriasis** and **trauma**.

Contd...

- **Koilonychia**: **Spoon shaped** nail; MC in **iron deficiency anemia**.
- **Onychogryphosis**: **Malalignment and thickening of nails**, such as, from, trauma or ill-fitting shoes.
- **Splinter hemorrhages**: Small brown linear streaks in the nail plate, **MC due to trauma**, also due to **nail psoriasis** and **subacute bacterial endocarditis**.
- **Pterygium of nail**: **Lichen planus**
- **Half and half nails (Lindsay's nails)**: White proximally and pink distally seen in **chronic renal failure** patients.
- **Beau's lines**: Transverse ridges (**horizontal ridging**) due to temporary interference with nail formation during **acute systemic illness**.
- **Terry's nails**: White nails with normal pink tips seen in **cirrhosis**.
- **Hippocratic nails**: Synonym for **clubbing of nails**.
- **Mee's lines on the nails**: Chronic **arsenic** poisoning.
- **Muehrcke nails**: A/w **hypoalbuminemia** and have two transverse parallel white bands, separated from each other and from the lunula by areas of normal pink nail.
- **Pachyonychia congenita**: Misshapen hypertrophic nails present since birth, AD.
- **Habit tic dystrophy**: Ridge and furrow pattern in center of nail.
- **Hyperpigmentation of nails**: May be caused by bleomycin, cyclophosphamide daunorubicin, doxorubicin, fluorouracil, hydroxyurea, melphalan, mechlorethamine, nitrosureas, zidovudine, taxanes, chloroquine, clofazimine, minocycline, tetracyclines, gold, tar.
- **Darier's disease**: Longitudinal white lines on nails, **V-shaped nick** at free margin of nails.
- **Blue nails**: **Chloroquine**; Wilson's disease (restricted to lunula); subungual hematoma.
- **Azure lunulae**: In **argyria**
- **Yellow nail syndrome**: **Pleural effusion; Sinusitis; Ankle and facial edema**.
- **Nail Patella syndrome**: Hypoplastic patella and nails. **Iliac horns** on X-ray.
- **Leukonychia**: Hypoalbuminemia.
- **Periungual telangiectasia** – seen in connective tissue diseases - scleroderma, SLE and dermatomyositis.

Pitting of nails

- **Skin disorders**: **Psoriasis, alopecia aerata**, hand **eczema**, trauma, idiopathic (Rare: parakeratosis pustulosa, pityriasis rosea, pemphigus vulgaris, dermatomyositis).
- **Infectious**: Paronychia, Tinea unguium, onychomycosis.
- **Congenital/hereditary**: Nail-patella syndrome; ectodermal dysplasia.
- **Systemic**: Hyperthyroidism, chronic renal failure, hemodialysis, sarcoidosis, secondary syphilis, Reiter syndrome.

CUTANEOUS MARKERS OF INTERNAL MALIGNANCY

Acanthosis nigricans

- **Velvety hyperpigmented thickened skin lesion**, prominent on the **darsum of the neck and major flexures (axillae or groin)**.
- **MC a/w adenocarcinoma stomach**; also other GIT malignancies.
- Also a/w **obesity, insulin resistance, acromegaly, Cushing's syndrome, polycystic ovary syndrome, insulin-resistant diabetes mellitus** (type A, type B, and lipotrophic forms) and **drugs** (diethylstilbestrol, nicotinic acid, glucocorticoids, growth hormones).
- **Histologically: papillomatosis** maybe seen in acanthosis nigricans.

- **Tripe palms**: **MC a/w Lung Ca**; if **both** tripe palms and acanthosis nigricans - **Gastric Ca** is MC.
- **Necrolytic Migratory erythema**: A/w **glucagonoma** syndrome.
- **Dermatomyositis**: MC a/w **Ca ovary**; also breast, lung, etc.
- **Erythema gyratum repens**: Hundreds of mobile concentric arcs that resemble the grain in wood; A/w **Carcinoma bronchus**.
- **Thrombophlebitis migrans**: Successive crops of tender nodules affecting blood vessels throughout the body, associated with **Ca pancreas** (especially body and tail tumors) - **Trousseau's syndrome**.
- **Paraneoplastic Pemphigus**: MC with **NHL**
- **Pyoderma gangrenosum**: Rarely a/w **leukemia**
- **Bazex syndrome**: Paraneoplastic acrokeratosis
- **Bowen's disease**: A form of **intraepidermal carcinoma**, MC on **head and neck**; next is **limbs**; **vulva** can be affected and so also **glans penis** (erythroplasia of **Queyrat**).
- **Others**: **Acquired ichthyosis; Sudden appearance of lanugo hair** (hypertrichosis lanuginosa), **multiple papillomata**; Cowden's disease (multiple hamartoma syndrome); **erythema annulare centrifugum**; **Sign of Leser Trelat** (sudden multiple seborrheic keratoses); **Sweet syndrome**; **Palmoplantar keratoderma**; **Pityriasis rotunda**; **extramammary Paget's disease**; **hypertrophic osteoarthropathy** and **digital clubbing**.

CRYOSURGERY

- Cryosurgery works on the principle of **freezing**. Freezing causes intracellular and extracellular ice crystals to form and the vascular stasis causes tissue anoxia and necrosis.

- The **most efficient** technique employs a **rapid freeze and slow thawing**.
- Agents used for cryosurgery are **liquid nitrogen** (MC – inexpensive, easy to store, easy to use, works quickly); **Freon 12**, **Freon 22**, **solid CO₂** (**‘dry ice’**), **liquid nitrogen**, and **liquid helium**.
- **Contraindications:** to cryosurgery are people with **cold-related conditions** such as cold urticaria, Raynaud’s disease, and cryoglobulinemia, and patients with heavily pigmented skin (as they may develop ugly scars).

Ultraviolet Radiation

- UV-A (long wave)** **320–400 nm**; absorbed in the dermis
- UV-B (medium wave)** **290–320 nm**; medical **MOST important**; causes most **photodermatoses**; used in **phototherapy** as **narrow band UV-B (311 nm)**; causes **skin tanning**
- UV-C (short wave)** **200–290 nm**; **MOST dangerous**; **NOT medically important** and **absorbed in the ozone layer** **does not reach the earth’s surface at all**.

FUNGAL SKIN INFECTIONS

Morphological Classification of Fungi

- **Phycomycetes:** They are lower fungi with **nonseptate hyphae** and form endogenous asexual spores called **‘sporangiospores’** contained within swollen sack like structures called **‘sporangia’**.
- **Ascomycetes** have septate hyphae and form sexual spores (ascospores).
- **Basidiomycetes** have septate hyphae and form sexual spores (basidiospores).
- **Fungi imperfecti** (deuteromycetes or hyphomycetes) contain fungi whose sexual phases have not been distinguished.
- These higher fungi have septate hyphae and make exogenous asexual spores called **‘conidia’**.
- Common culture media used in mycology are **Sabouraud’s dextrose agar**, **Corn Meal agar** and **Czapek-Dox medium**.
- Fungal morphology - studied by staining with **PAS stain**.

DERMATOPHYTOSIS (RINGWORM, TINEA)

- Dermatophytes are classified as:
 - **Anthropophilic** (restricted to humans)
 - **Zoophilic** (found in animals but infect humans exposed to animals): Examples are *Microsporum canis*,

- M. equinum*, *M. nanum*, *M. persicolor*, *Trichophyton equinum*, *T. mentagrophytes*, *T. sinuii*, *T. verrucosum*
- **Geophilic** (found in soil): Examples are *M. gypseum*, *T. ajelloi*, *T. terrestre*
- Three genera of dermatophytes infecting skin, hair and nails are:
 1. **Trichophyton** (affects **all three** - skin, hair, nails)
 2. **Microsporum** (affects **hair and skin**)
 3. **Epidermophyton** (affects **skin and nails**).
- Clinically: All tinea/ringworm infections are superficial (It is a **keratinophilic** fungus); they are characterized by **annular (ring shaped)** lesions with **peripheral scaling** that spreads outwards (**central clearing**).
- Also remember in MCQs that, **central scarring = lupus vulgaris** and **central crusting = leishmaniasis**.

MC organisms

- MC cause of all Tineas (**apart from** Tinea capitis) = **Trichophyton rubrum**.
- MC cause of **tinea capitis**
 - In **India**: *Trichophyton violaceum*
 - In **Europe**: *T. tonsurans*
 - In **US/UK**: *Microsporum canis*.

Tinea Pedis (Athlete’s Foot)

- **MC** type of Tinea **worldwide**.
- A/w **sweaty feet** and **shoes/socks**.
 - **Interdigital** type **is MC** and involves the **4th web space** MC.
 - **Moccasin** type involves the **soles**.
 - **Bullous** type: causes severe inflammatory blisters - caused by *Trichophyton interdigitale* (earlier called *T. mentagrophytes*).

Tinea Unguium (Nails)

- **Yellow discolored nails**, **tunneling of nail plate**; thickened **nail plate**; subungual hyperkeratosis.
- Do KOH mount of nails scrapings.

Tinea Capitis (Hair and Scalp)

- MC in **children** with **easily pluckable hairs** causing **patchy alopecia** and **broken hairs**.
- **Endothrix**: Fungal spores inside hair shaft; **Black Dot** - caused by *Trichophyton violaceum/mentagrophytes*.
- **Ectothrix**: Fungal spores outside hair shaft; **Gray patch** caused by *Microsporum*
- **Kerion**: A highly inflammatory **pustular** infection causing **boggy scalp swelling** caused by *T. verrucosum*,

- **Favus**: Caused by *Trichophyton schoenleinii*, **honey-comb scutula** or **crusts** seen, permanent scarring and scalp hair loss.
- **Piedra**: Refers to adherent deposits on the hair shafts.
 - **Black piedra** - caused by *Piedraia hortae*.
 - **White piedra** - caused by *Trichosporon beigelii*.
- **Gray patch and Favus** fluoresces on **Wood’s lamp** - **green color**.

‘Tineas’ by location

- **Tinea manuum** (hands)
- **Tinea corporis** (trunk)
- **Tinea barbae** (beard)
- **Tinea cruris** (jockey’s itch, **dhobi’s itch**): groin or perianal region (usually sparing the trunk)
- **Tinea faciei**: of face
- **Tinea nigra**: A superficial dermatomycosis caused by *Phaeo- onellomyces (Exophiala) werneckii*; a pigment-producing fungus. It causes an asymptomatic brown or black patch on the **palm and soles**
- **Tinea incognito**: Extensive tinea with an atypical appearance due to inappropriate use of topical **corticosteroids**

Treatment

- **Tinea unguium (nails)** requires **4–6 months** of treatment! For all ordinary ringworm (tinea) of skin - topicals are effective - **azoles; terbinafine, ciclopirox olamine**.
- For **multiple areas** involvement and where **systemic antifungals** are required - **DOC is terbinafine** (has now replaced griseofulvin).

EXTRA EDGE

- **Majocchi’s granuloma** - This is a follicular abscess produced when a dermatophyte infection **penetrates the follicular wall into the surrounding dermis**. Commonly seen as boggy papules or plaques on the legs and sometimes on the arms. *T. rubrum* or *T. mentagrophytes* are isolated from these lesions. Treat with oral antifungals.
- Fungi responsible for **fluorescent tinea capitis** are - *T. Schoenleinii*, *M. Canis*, *M. Audouinii*, *M. Distortum*, *T. Ferrugineum* (**‘See Cats And Dogs Fight’**).
- **‘Id’ reaction**: An allergic reaction to circulating dermatophytes antigens released by dying fungi during antifungal treatment. Characterized by sterile skin vesicle formation distant from primary site, example: Tinea pedis with subsequent hand lesions.

Tinea/Pityriasis Versicolor

- **MC** caused by **Malassezia globosa** (also caused by *M. furfur* - was MC earlier).

- Presents as **oval, scaly, macules** on the **chest, shoulders and back**.
- On dark skin, they appear **hypopigmented** and in untanned Caucasians they appear **hyperpigmented**!
- **‘Coup d’angle’** sign of **Besnier (stroke of nail, scratch sign)** is seen - **loosening of scales by scratching with fingernail**.
- **KOH preparation** from scaling lesions will show short **cigar-butt hyphae** and round spores, the so-called **‘spaghetti and meatballs’** or **‘bacon and eggs’** appearance.
- Under **Wood’s light** the lesions **DO NOT** fluoresce or appear **golden yellow/coppery-orange**.
- **Selenium sulfide shampoo 2.5%** or **ketoconazole** shampoos are usually effective treatment.
- For widespread infection: oral **ketoconazole** or **fluconazole**.
- Note: **Catheter-acquired sepsis** due to *M. furfur* develops in patients (esp. neonates) **receiving intravenous lipid**.
- Note: **Pityriasis capitis** is commonly known as **‘dandruff’**.

COLORS UNDER WOOD’S LAMP

- **Wood’s lamp** is made up of **nickel oxide and silica**.
- It generates **360-nm ultraviolet (or ‘black’) light**.

Condition	Color
Erythrasma	Coral red
Tinea capitis by <i>Microsporum canis/audouinii</i>	Brilliant green
<i>Pseudomonas</i> infection	Pale blue/green
Vitiligo	Totally white
Tinea versicolor	Dull yellow
Tuberous sclerosis	Blue white
Porphyria cutanea tarda	Pinkish red (urine)

BLISTERING SKIN DISEASES



Fig. 26.35: Woods lamp

Classification Based on Etiology

- Congenital: *Hailey-Hailey* disease; *Darier's* disease (keratosis follicularis) and *Congenital epidermolysis bullosa*.
- Acquired - discussed in elaborate table here.

Classification Based on Level of Blister

Intraepidermal	
Suprabasal (above basal layer)	<ul style="list-style-type: none">▪ Pemphigus vulgaris▪ Pemphigus vegetans▪ Pemphigus erythematosus▪ Paraneoplastic pemphigus
Subcorneal (below stratum corneum)	<ul style="list-style-type: none">▪ Pemphigus foliaceus▪ Subcorneal pustular dermatosis (SCPD)▪ Staphylococcal SSS (SSSS)
Subepidermal	
	<ul style="list-style-type: none">▪ Bullous pemphigoid▪ Cicatricial pemphigoid▪ Herpes (pemphigoid) gestationis▪ Dermatitis herpetiformis▪ Linear IgA disease▪ Epidermolysis bullosa acquisita (EBA)

General Clinical Features of Blistering Diseases

- Clinically they are characterized by **morbidity** (pain, pruritus, disfigurement) and **mortality** (largely due to loss of epidermal barrier function and/or secondary infection).
- **Blister formation** is due to loss of cohesion between epidermal cells (**acantholysis**).
- The mainstay of **treatment** is **systemic glucocorticoids** ± **immunosuppressives**.

Direct Immunofluorescence (DIF)

- DIF detects the abnormal antibody deposition in autoimmune blistering diseases by tagging with immunofluorescent dyes; it is the **DIAGNOSTIC** test for the blistering diseases described below (**except** congenital diseases - Hailey, Darier's and Cong, epidermolysis bullosa)
- Biopsy is taken from **perilesional skin**.
- The patterns in various diseases are given in following table:

Disease	DIF pattern
Pemphigus (all types)	Fishnet pattern (IgG and C3 deposits)
Bullous pemphigoid; Cicatricial pemphigoid; EBA	Linear, homogenous deposits of IgG and C3 at the DEJ (dermoepidermal junction)
Dermatitis herpetiformis	Focal granular deposits of IgA at tips of dermal papillae
Linear IgA disease	Linear, homogenous deposits of IgA at the DEJ

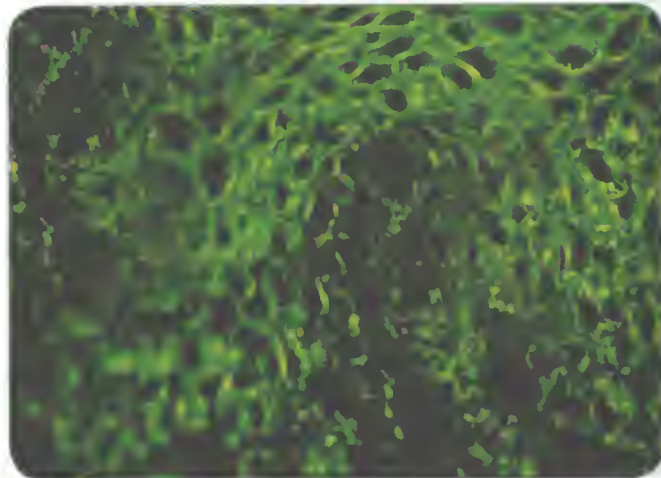


Fig. 26.36: Direct immunofluorescence of pemphigus: fish-net like deposit of IgG in epidermis

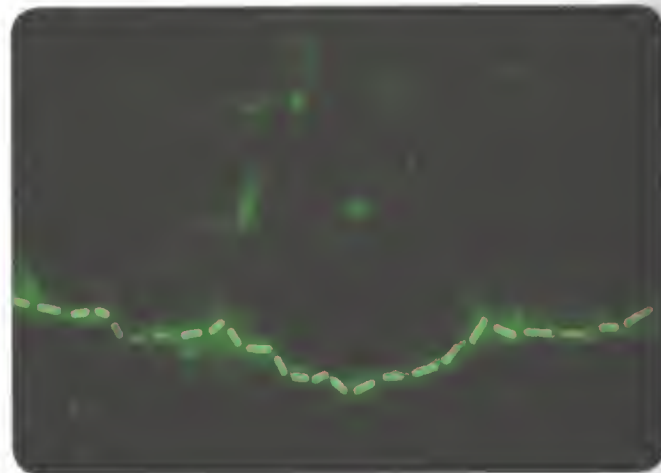


Fig. 26.37: Direct immunofluorescence of bullous pemphigoid: linear deposit of IgG and C3 along the basement membrane

ACQUIRED BLISTERING DISORDERS

Clinical features	Remarks
Pemphigus vulgaris (PV)	
<ul style="list-style-type: none">▪ Flaccid blisters which rupture easily▪ Nikolsky's sign +ve and Asboe-Hansen (bulla spread) sign +ve▪ Mouth first gets involved (~90% have oromucosal involvement) - then skin <i>after few months</i> (scalp, face, neck, axilla, trunk affected)▪ Lesions usually heal without scarring▪ Pemphigus vegetans: rare variant of PV with vegetating (<i>cauliflower like</i>) masses.	<ul style="list-style-type: none">▪ HP: Suprabasal blister; 'Row of tombstones' - basal keratinocytes remaining attached to DEJ and appear like tombstones on a grave▪ DIF: see table above▪ Antibodies: Antidesmoglein antibodies seen: anti-Dsg3 (Also anti-Dsg1 in patients with skin involvement)▪ Note: Pemphigus is derived from the Greek word 'pemphix' - meaning 'bubble/pustule'.
Pemphigus foliaceus (PF)	
<ul style="list-style-type: none">▪ Flaccid bullae (very flaccid and superficial so that intact blisters NOT seen) BUT crusts and shallow erosions seen in seborrheic areas (scalp, central-face, neck, upper chest, and back).▪ Mucosa NOT involved▪ Nikolsky sign +ve; Bulla spread sign - negative▪ Maybe a/w thymoma/myasthenia▪ Drug induced pemphigus resembles PF (penicillamine MC, captopril, rifampin, piroxicam, penicillin, phenobarbital)	<ul style="list-style-type: none">▪ HP: Subcorneal blister▪ DIF: see table above▪ Antibodies: Anti-Dsg1▪ Fogo selvagem = endemic form of PF in Brazil▪ Senear usher syndrome: Pemphigus erythematosus-a localized form of PF that resembles SLE
Paraneoplastic pemphigus (PNP)	
<ul style="list-style-type: none">▪ A/w Non-Hodgkin's lymphoma (MC), CLL, thymoma, spindle cell tumors, Waldenstrom's macroglobulinemia, and Castleman's disease.▪ PNP maybe a/w bronchiolitis obliterans.▪ Severely painful stomatitis (<i>oral lesions</i>) that are classically resistant to therapy▪ Polymorphic lesions: blisters, erosions, erythema, etc.	<ul style="list-style-type: none">▪ HP: Suprabasal blister; vacuolar interface dermatitis▪ Antibodies: Anti-Dsg1 and Dsg3; Antiplakin autoantibodies [desmoplakins I and II, Bullous Pemphigoid Antigen 1 (BPAG1) envoplakin, periplakin, and plectin]
Bullous pemphigoid (BP)	
<ul style="list-style-type: none">▪ Initially itchy urticarial plaques▪ Tense blisters on flexor surfaces on normal looking or erythematous skin; blisters heal fast▪ Oromucosal lesions are RARE▪ Affects elderly age (65-75 years)▪ Nikolsky sign - ve; Bulla spread sign +ve.	<ul style="list-style-type: none">▪ HP: Subepidermal, non-acantholytic blister; (BULLous: BeLOW epidermis)▪ DIF: see table above▪ Antibodies: Anti BPAG1 (BP230) and BPAG2 (BP180) antibodies
Cicatricial pemphigoid	
<ul style="list-style-type: none">▪ Blisters are similar to BP▪ Mucosal scarring occurs: Oral > conjunctival	<ul style="list-style-type: none">▪ HP: Subepidermal blister▪ Antibodies: Anti BPAG2 (MP 180) and anti-laminin 332 antibodies
Dermatitis herpetiformis (DH)	
<ul style="list-style-type: none">▪ Extremely itchy small papules and vesicles on extensor surfaces (elbows, knees, buttocks, and posterior nuchal area)▪ A/w gluten sensitive enteropathy (celiac sprue) and triggered by potassium iodide also▪ A/w HLA B8/DRW3 and HLA DQW2▪ Treatment: Dapsone is the DOC▪ Strictly exclude gluten from the diet▪ Risk of GI lymphoma	<ul style="list-style-type: none">▪ HP: Subepidermal blister; neutrophils in tips of dermal papillae (<i>papillary tip microabscesses!</i>)▪ Antibodies: against epidermal transglutaminase 3 and antilendomysial antibodies▪ DIF: see table above
Epidermolysis bullosa acquisita	
<ul style="list-style-type: none">▪ Characterized by blister formation due to trauma	<ul style="list-style-type: none">▪ HP: Subepidermal blister▪ Antibodies: against type 7 collagen

Contd...

Clinical features	Remarks
Linear IgA bullous dermatosis (linear IgA disease)	

- | | |
|---|--|
| <ul style="list-style-type: none">▪ Itchy small papules on extensor surfaces can resemble DH or BP▪ Called <i>chronic bullous disorder of childhood (CBDC)</i> when occurring in childhood▪ Tense blisters form a 'string of jewels/cluster of pearls' appearance▪ Sites: perineum and perioral areas; mucus membranes affected in 50% cases▪ Dapsone is DOC | <ul style="list-style-type: none">• HP: Subepidermal blister• Antibodies: Against LAD antigen (BP120); BPAG1 or BPAG2 |
|---|--|



Fig. 26.38: Pear sign: positive in pemphigus vulgaris, collection of fluid in the lower part of the bulla



Fig. 26.39: Bulla-spread sign: positive in pemphigus vulgaris. Note sharp edge



Fig. 26.40: Bullous pemphigoid: large tense bullae on urticarial base



Fig. 26.41: Pemphigus foliaceus: scale-crusts in seborrheic distribution



Fig. 26.42: Dermatitis herpetiformis: grouped excoriations and intervening vesicles over both elbows

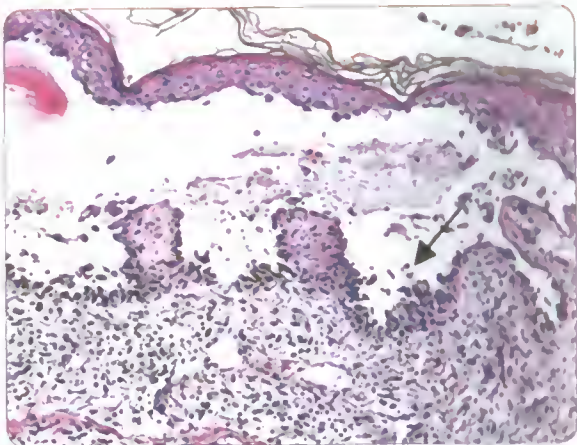


Fig. 26.43: Histopathology of pemphigus vulgaris: suprabasal intraepidermal split with acantholysis

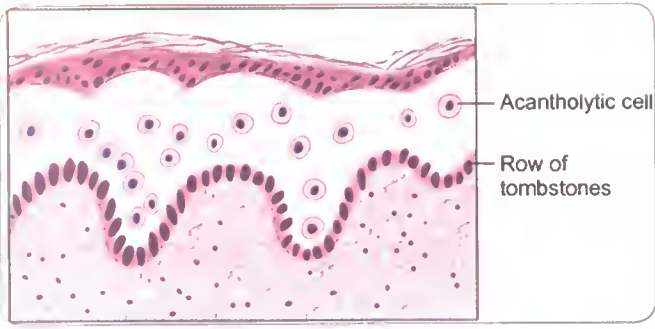


Fig. 26.44: Pemphigus vulgaris. Diagrammatic histopathological findings

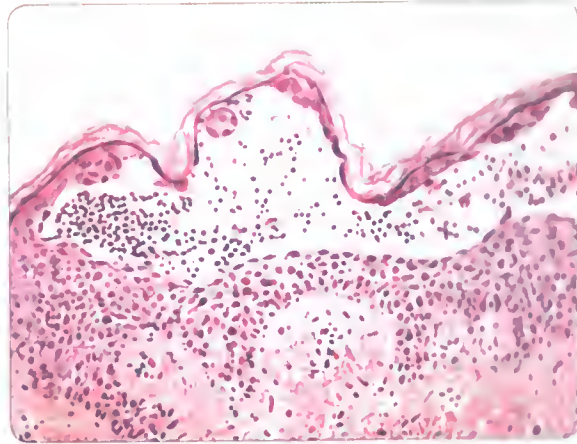


Fig. 26.45: Histopathology of pemphigus foliaceus: subcorneal split containing acantholytic cells and eosinophils

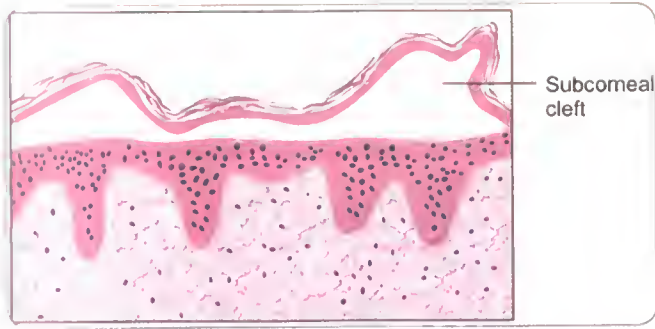


Fig. 26.46: Pemphigus foliaceus. Diagrammatic histopathological findings

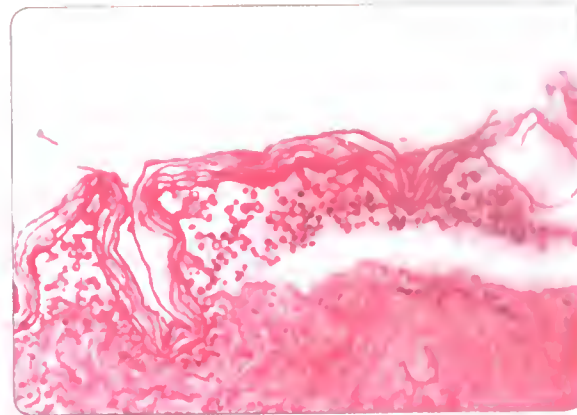


Fig. 26.47: Histopathology of bullous pemphigoid: subepidermal bulla with eosinophils

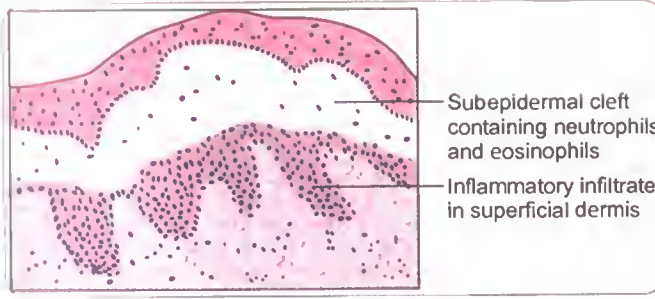


Fig. 26.48: Bullous pemphigoid. Diagrammatic histopathological findings

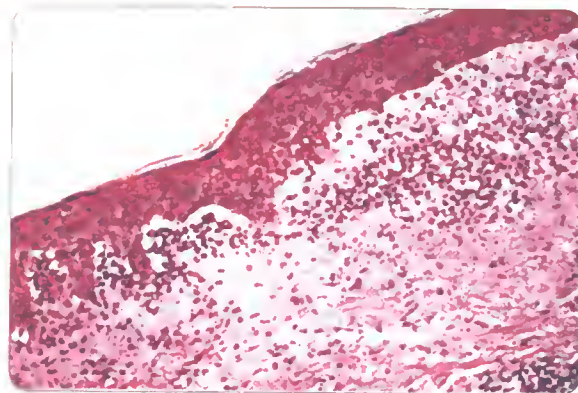


Fig. 26.49: Histopathology of dermatitis herpetiformis: subepidermal split with papillary apical abscesses containing large number of neutrophils. Top (10x). Bottom (40x)

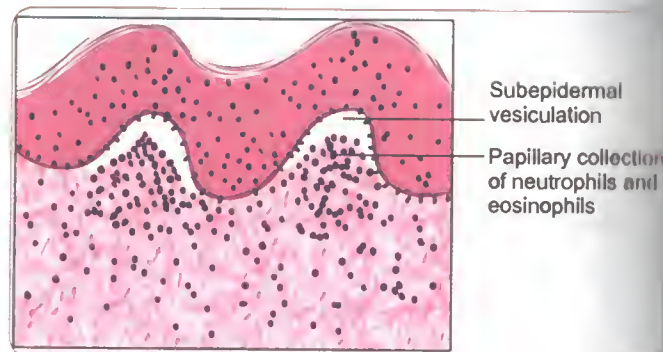


Fig. 26.50: Dermatitis herpetiformis. Diagrammatic histopathological findings

INHERITED BLISTERING DISORDERS

Hailey-Hailey disease

- Aka **Chronic benign familial pemphigus**.
- **AD; ATP2C1** gene defect (defect in **calcium pump in Golgi apparatus in keratinocyte**).
- Recurrent **vesicles, pustules** in **flexures** (neck, axilla, groin, inframammary areas) - may create **fissures**.
- **HP: Suprabasal blisters** due to **incomplete acantholysis** - keratinocytes appear still connected to each other giving appearance of a '**dilapidated/broken brick wall**'
- Treatment: Corticosteroids.

Darier's Disease Keratosis Follicularis (Darier's Disease)

- AD, a/w Pruritus
- **ATP2A2 gene defect** (defect in **calcium ATPase** in endoplasmic reticulum in keratinocytes)

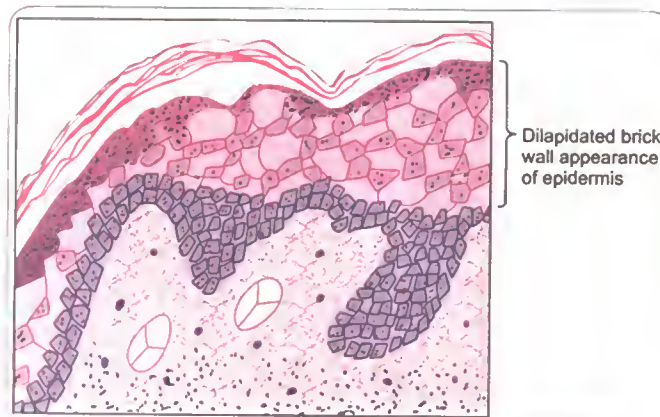


Fig. 26.51: Diagrammatic histological findings in Hailey-Hailey disease

- **Hyperkeratotic greasy/warty papules** common in the **seborrheic areas** (forehead, scalp margin, scalp, nasolabial folds, ears, chest and back) and palms
- Also affects **nails** (longitudinal red and white nail ridges and split, **V-shaped nick** at the free margin of the nail)
- Mucosal lesions in the mouth with a **sandpaper** texture.
- **HP: Acantholysis** and **dyskeratosis**; 2 types of dyskeratotic cells are present: **corps ronds** and **corps grains**
- Treatment: Sunscreens; oral retinoids (isotretinoin).

Congenital Epidermolysis Bullosa

- Genetic skin fragility - **Trauma induced skin blisters** in trauma prone areas like hands, feet, knees, elbows throughout life.
- Types:
 - **EB simplex (AD)** - **Keratin K5 and K14** defect.
 - **Junctional EB (AR)** - **laminin** defect
 - **Dystrophic EB (AR)** - **Collagen 7** defect.
- Diagnosis: DIF is negative; **Electron microscopy** is required.

Nikolsky and Friends: Mechanical Signs in Bullous Disorders

Bulla spread sign: aka Asboe-Hansen sign	+ve in Pemphigus (sharp edge), BP (rounded edge), DH, EBA, CP, DEB, SJS and TEN. -ve in Hailey-Hailey disease and SSSS	Extension of blister in direction opposite to side of pressure
Nikolsky sign (Means: Intra-epidermal bulla and disease active)	+ve in Pemphigus; SSSS; TEN; Porphyria; SJS	Peeling off of clinically normal skin due to acantholysis

Contd...

Contd...

Pseudo-Nikolsky sign (Means: Intra-epidermal bulla)	+ve in SJS, TEN and in some cases of burns and bullous ichthyosiform erythroderma, erythema multiforme	Peeling off of skin due to apoptotic necrosis
Pear sign (Means: Intra-epidermal flaccid bulla)	+ve in Pemphigus	Collection of fluid in lower part of blister due to gravity
Sheklakov sign (Means: Sub-epidermal bulla)	+ve in in subepidermal blistering disorders, like BP, CP, herpes gestationis, DH, linear IgA bullous dermatitis, EBA, junctional and DEB, porphyrias and bullous SLE	Pinpoint bleeding spots on peeling off of the remnant of blister (analogous to Auspitz sign)

Key: BP = Bullous pemphigoid; CP = Cicatricial pemphigoid; DH = dermatitis herpetiformis; DEB = Dystrophic epidermolysis bullosa; SJS = Stene Johnson syndrome; TEN = Toxic epidermal necrolysis; SSSS = Staphylococcal scalded skin syndrome

LINES IN DERMATOLOGY

Blaschko's Lines

- **Correspond to the pathways followed by keratinocytes** migrating from the neural crest **during embryogenesis**.
- Diseases following Blaschko's lines: **incontinentia pigmenti, lichen striatus, linear lichen planus, inflammatory linear verrucous epidermal nevus, Blaschko dermatitis (adult equivalent of lichen striatus), Goltz syndrome**.

Wallace's Lines

- A **demarcation line** on the **lateral aspect of palms and soles**, where the glabrous (i.e. skin devoid of hair) plantar or palmar skin meets hairbearing dorsal skin.
- Diseases displaying sharp cutoff at Wallace's line = Lichen planus, pompholyx (vesicular eczema) and rash of Kawasaki's disease.

Langer's Lines

- **Cleavage lines** correspond to the alignment of collagen fibers within the dermis. Surgical incisions carried out along Langer's lines heal with less scarring than those made across the lines.

Vogt Fitcher's Lines

- **Pigmentary demarcation** lines between the darker dorsal and paler ventral surfaces.

Kraissl Lines

- These are oriented **perpendicular** to the action of the underlying muscles. They usually coincide with the **wrinkle lines**.

Borges Lines

- These are **relaxed skin tension lines** which follow furrows formed when the skin is relaxed and are produced by pinching the skin.

SWEAT GLAND DISORDERS

Miliaria (Prickly Heat)

- Due to obstruction of **eccrine** sweat glands
- **Miliaria rubra (prickly heat)**: red inflamed papules with pricking sensation
- **Miliaria crystallina (sudamina)**: crystal like vesicles after fever.
- **Miliaria profunda**: larger inflamed papules.

Hidradenitis Suppurativa

- Chronic **suppurative** condition of **apocrine** sweat glands and **hair follicles**.
- Affects **axilla**, inguinal and anogenital regions.



Fig. 26.52: Hidradenitis suppurativa, early lesion: multiple 'blind' boils

Bromhidrosis

- **Malodorous sweating** due to bacterial degradation of apocrine sweat.

- **Fish odor syndrome:** excretion of *trimethylamine* in eccrine sweat, urine and saliva; **avoid garlic** in diet.

Chromodrosis

- **Colored sweat** due to *lipofuscin* in sweat.

Fox-Fordyce Disease (Apocrine Miliaria)

- Itchy follicular papules in apocrine areas - **axillae MC** and groin; **MC in women** aged 13–35 years.

Fordyce spots

- **Ectopic sebaceous glands** on **lips, oral mucosa** and **penis** - normal condition.
- **Tyson's glands** are Fordyce spots on the penis.

DRUG-INDUCED SKIN REACTIONS

- Drug induced skin reaction **MC starts on the trunk**.

Cutaneous Drug hypersensitivity	HLA association
Carbamazepine	HLA B*1502
Abacavir	HLA B*5701
Allopurinol	HLA B*5801

INFESTATIONS

Scabies

- **Etiology and spread:** Caused by *itch mite, Sarcoptes scabiei*; spread through **contact (crowding, uncleanliness sexual promiscuity)** with infected individuals, spread is common in **families crowding, uncleanliness**.
- **Clinically:**
 - Intense **pruritus** that **worsens at night and after a hot shower**.
 - **Burrows** appear as dark wavy lines in the **epidermis** that measure 3 to 15 mm and end in a small pearly bleb that contains the **female mite**.
 - **Papulovesicular** lesions are seen on **interdigital webs, flexor aspects of wrists**, the elbows, axillae, around the nipples, umbilicus, groin area (imaginary line joining these regions is **Circle of Hebra**), legs and feet.
 - The **face, scalp, neck, palms and soles** are **SPARED** except in children.
 - **'Hang Glider sign'**: Dark triangular biting apparatus of *Sarcoptes scabiei* seen at the end of subcorneal tunnel.

Varieties of scabies:

- **Norwegian (crusted) scabies:** Hyperinfestation with millions of mites, may result from glucocorticoid use, immunodeficiency or AIDS.
- **Scabies incognito:** Occurs in persons treated with steroids; **Sarcoptic mange:** animal scabies; **Nodular scabies:** is seen in **scrotum** and axilla.
- **Treatment:**
 - **All the family members** to be treated at the **same time**. It is a **water-washed disease**—encourage personal hygiene and washing.
 - **5% permethrin cream** applied from the neck down after bathing and removed 8h later with soap and water; topical alternatives include *benzyl benzoate*, *sulfur ointment*, *crotamiton cream* (*Lindane NOT used now*).
 - **Ivermectin** single oral dose is effective treatment in resistant cases.
 - **In pregnancy-permethrin is drug of choice**.



Fig. 22.53: Scabies Mite

Pediculosis (Lice Infestation)

- **Head Lice:**
 - *Pediculus humanus capitis*; spread is by **direct head-to-head contact**. **Intensely pruritic** (due to louse's saliva).
- **Body lice:**
 - *Pediculus humanus corporis*; body lice remain in clothing except when feeding and cannot survive more than a few hours away from the human host.
 - Pruritic lesions common below the neckline.

- **'Vagabond's disease':** Chronic infestation resulting in postinflammatory hyperpigmentation and thickening of the skin.
- **Pubic (Crab) lice:**
 - *Phthirus pubis*; transmitted mainly by sexual contact; infests pubic and axillary hair.
 - **Blepharitis** due to eyelash infestation of *Phthirus pubis* is called **Phthiriasis palpebrarum**.
 - Intensely pruritic lesions and **blue macules (maculae ceruleae)** develop at the site of bites.
- **Treatment:**
 - Preferred treatment is **1% permethrin cream rinse (kills both lice and eggs)**; 0.5% malathion lotion (less effective, inflammable).
 - **Phthiriasis palpebrarum:** Petrolatum ointment and picking of the nits manually from eyelashes.
 - **Disinfection of combs and brushes, dispose infested bedding and clothes.**

Cutaneous larva migrans (creeping eruption)

- Caused by **hookworm** (nematodes) *Ancylostoma braziliense* (**MC**), *A. caninum*, *Necator americanus*, *Strongyloides stercoralis* (**'larva currens'**), *Gnathostoma*, *Gasterophilus*.
- It presents as an **erythematous, serpiginous, pruritic** cutaneous eruption caused by **percutaneous penetration** and subsequent **migration of larvae**.
- The **treatment of choice** is **topical thiabendazole**; oral **ivermectin**, **albendazole** may be used in rare cases.



Fig. 26.54: Larva migrans. Creeping serpentine thread-like eruption on abdominal wall

Insect Bite Hypersensitivity

- **Pruritic excoriated papules** on forehead and **exposed parts** of body (arms and legs) due to mosquito, flea bites; MC in **children**.
- **Recurring** every year during the **rainy season**.
- Treat with antihistamines and mild corticosteroid ointments.

Leishmaniasis

1. Cutaneous Leishmaniasis

- **Old world Leishmaniasis** (Aka: *Baghdad boil*; *Oriental sore*; *Delli boil*; *Aleppo boil*; *Kandahar sore*; *Lahore sore*)
- Caused by *L. major* or *L. tropica*
- Transmitted by bite of **sandfly (phlebotomus)**
- **Erythematous nodule/plaque** which ulcerates and gets **crusted** - compared to a volcano with a crater like ulcer (**'volcano sign'**).
- **New world Leishmaniasis** (Aka *Chiclero's ulcer*)
 - Caused by *L. mexicana* or *brasiliensis*
 - Transmitted by sandfly (*Lutzomyia*).
 - **Lesions** similar to above
- Biopsy: extra and intracellular amastigotes called **Leishman Donovan** bodies.
- Diagnosis is by culture on **NNN medium** - Nicole-Novy-MacNeal medium.

2. Visceral Leishmaniasis

- Caused by *L. donovani*
- Presents with high **fever, anemia/leucopenia, splenomegaly**
- Skin lesion - nodule at site of fly bite; **'Kala Azar'** means **'Black fever'** - due to darkening of the skin at site of bite.

3. Post Kala Azar Dermal Leishmaniasis (PKDL)

- **MC** skin manifestation of Leishmaniasis in **India** - closely **resembles Hansen's disease**.
- Develops 1–2 years after recovery from leishmaniasis.
- Maybe **hypopigmented macules** on face/arms/trunk OR papules/nodules.

Treatment of Leishmaniasis

- **Oral miltefosine** > **Liposomal amphotericin B** is the **DOC**.

KEYWORDS

'Sawtoothed'	Lichen planus
'Ball and claw'	Lichen nitidus (also see histiocytes)
'Swarm of bees'	Alopecia areata
'Toy soldiers'; 'String of pearls'; 'Fettuccine collagen'	Mycosis fungoides
'Coat-sleeve' perivascular lymphocytosis	Gyrate erythema (consider lymphocytic vasculitis)

Contd...

'Tea cup' scale/Tea cup sign (oblique, upwardly angulated parakeratosis)	Pityriasis rosea
'Dirty feet'	Solar lentigo (vs 'dirty fingers' – lentigo simplex), Becker's nevus

Contd...

Contd...

'Bubbligum stroma'	Neurofibroma
'Glassy collagen'	Keloid
'Tadpoles/sperm in the dermis'	Syringoma (if clear cell variant, think diabetes)
'Corn flakes'	Keratin granuloma
'Red crayons' (blood vessels)	Atrophie blanche

PHENOMENA

Phenomenon	Seen in	Remarks
Reynold's Braude phenomenon	<i>Candida</i> infection	Incubation of the culture of <i>Candida</i> species with human or sheep serum at 37°C produces germ tubes within 2-4 h
Splendore-Hoeppli phenomenon	<i>Actinomyces</i> , fungi, bacteria, and parasitic infection	Intensely eosinophilic material (radiate, star-like, asteroid or club-shaped configurations) around the microorganisms or biologically inert substance
Pagetoid phenomenon	Pathognomonic for melanoma ; also seen in apocrine gland carcinoma	'Upward spreading' of melanocytes into the epidermis
Lucio phenomenon	Diffuse, infiltrative, nonnodular lepromatous leprosy	Characterized by arteritis and ulcers on legs
Koebner/Isomorphic phenomenon	Psoriasis	Appearance of new lesions in uninvolved skin due to trauma
Reverse Koebner phenomenon	Psoriasis	Area of psoriasis clears after injury (like dermabrasion or surgery)
Ranbok phenomenon (inverse Koebner)	Psoriasis with alopecia areata	
Kaebner's Pseudaisamorphic phenomenon	Infectious diseases, e.g. warts, molluscum contagiosum, Behcet's disease and pyoderma gangrenosum	
Isotopic phenomenon (Wolf's Isotopic response)	Herpes zoster	Occurrence of a different or unrelated skin disease at the site of the healed disease
Broca's phenomenon	Lichen planus	Subepidermal hemorrhage , which occurs on careful scraping of a classical lesion of lichen planus
Nikolsky's phenomenon	Pemphigus vulgaris; Porphyria; Steven Johnson's; Toxic epidermal necrolysis; Staphylococcal scalded skin syndrome	When the superficial layer of the epidermis is felt to move over the deeper layer, and instead of immediately forming erosion as in Nikolsky's sign, a blister develops after some time; it indicates a lower disease activity than that of patients who have a positive Nikolsky sign
Pathergy phenomenon	Behcet's disease; pyoderma gangrenosum	Heavy neutrophilic infiltrates or pustular reaction that develop at the site of non-specific trauma (sterile needle prick)

PANNICULITIS

- Panniculitis represents **infiltration of subcutaneous tissue** by inflammatory and/or neoplastic cells. This condition presents clinically as an apparent deep **induration** or swelling of the skin.
- Major forms of panniculitis are:
 - **Septal** panniculitis – **erythema nodosum**

- **Lobular** and mixed panniculitis – vasculitis (**erythema induratum**) and connective tissue disease (**lupus panniculitis or lupus profundus**).
- Metabolic derangements
 - **Sclerema neonatorum** – seen in **premature infants** and is characterized by diffusely cold, **rigid, board-like skin**; early death is common

- **Subcutaneous fat necrosis of the newborn** – relatively firm discrete subcutaneous nodules develop several weeks after birth; hypercalcemia may be present; the prognosis for survival and resolution of lesions is excellent. The microscopic changes of **post-steroid panniculitis** are virtually identical to those of subcutaneous fat necrosis of the newborn.
- **Pancreatic (enzymatic) fat necrosis**
- **Alpha-1-antitrypsin deficiency panniculitis**
- **Traumatic panniculitis, Infectious panniculitis, Malignancy and panniculitis, Lipodystrophy.**

DERMATOLOGIC THERAPY

Historical Topical Solutions

	Composition	Use
Calamine lotion	Calamine, ZnO, bentonite, sodium citrate, glycerine, aqua	Antipruritic and soothing agent for mild edematoses
Castellani's paint	Boric acid, carbol fuchsin, resorcinol, acetone, ethyl alcohol, phenol	Fungal infections
Modified Whitfield paint	Salicylic and benzoic acid, copper sulphate, glycerine	Fungal infections
Lassar's paste	ZnO, salicylic acid, Starch	Subacute dermatoses
Candy solution	KMnO4 solution	Antiseptic, astringent
Burrow ointment	Aluminium acetate	Antibacterial
Lotio alba	Potassium sulphate, zinc sulfate, resorcinol	

Chemical Peeling Agents

- **Glycolic acid**
- **TCA** (trichloroacetic acid)
- Jessner's solution
- Resorcinol
- Baker Gordon phenol formula
- Solid CO₂
- Pyruvic acid
- Phenol

Demelanizing/Depigmenting Agents

- Kojic acid 2% cream
- Hydroquinone

- Monobenzyl ether of hydroquinone
- Azelaic acid
- Glycolic acid
- Retinoic acid
- Magnesium ascorbyl phosphate.

Sunscreens

- **Organic (chemical) sunscreens:** **Para-aminobenzole acid (PABA)** absorbs UVB; rarely used now
- **Inorganic (physical) sunscreens:** Titanium dioxide; zinc oxide, kaolin, talc; deflect light or prevent light entry.
- **SPF: Sun protection factor**, a measure of protection provided by sunscreen against UVB. It is a ratio.

Anti-inflammatory Agents

- **Topical corticosteroids** (in decreasing order of potency)
 - Clobetasol propionate (superpotent)
 - Halobetasol propionate
 - Betamethasone dipropionate
 - Fluocinonide
 - Mometasone
 - Fluticasone
 - Triamcinolone
- **Topical calcineurin inhibitors:** inhibits synthesis of IL-2 effectively inhibiting activation and proliferation of T lymphocytes.
 - Tacrolimus
 - Pimecrolimus

Keratolytic Agents

- Act by removing keratin
- Hydroxy acids: Alpha (glycolic acid, lactic acid, pyruvic acid) and beta (salicylic acid).
 - Urea 20-40%
 - Resorcinol
 - Retinoic acid

Keratoplastic Agents

- Restore abnormal keratinization process to normalcy
- Coal tar
 - Anthralin
 - Retinoic acid (vitamin A acid, tretinoin).

Grenz Ray Therapy

- Aka **Bucky ray** or **Border ray** therapy.
- They are **ultrasoft radiation** produced at **low kilovoltage** that penetrate only into **first 2 mm of skin**.

- They appear to *reduce number of Langerhans cells* thus having an **anti-inflammatory (calming)** effect, they are NOT superficial radiotherapy used for skin cancers.
- This therapy is *rarely used these days* due to availability of better therapies.
- However, it is used for skin conditions **unresponsive to conventional treatments**, e.g. unresponsive scalp psoriasis, eczema, acne, pruritus ani, etc.
- **Strachan's syndrome:** Painful sensory polyneuropathy, optic neuropathy, hearing loss, orogenital ulceration.
- **Pitted keratolysis** is caused by a cutaneous infection with *Micrococcus sedentarius* (now renamed to *Kytococcus sedentarius*); *Dermatophilus congolensis*; or species of *Corynebacterium*, *Actinomyces*, or *Streptomyces*.
- **Chlorhexidine, isopropyl alcohol and povidone iodine** are commonly used skin antiseptics.
- Chloasma (melasma): MC in *females* on the **bridge of the nose and cheeks**; acquired **hypermelanosis** exacerbated by **sun exposure, pregnancy, OCPs** and antiepilepsy drugs.
- In **burns, subepidermal bulla** are seen (in *superficial dermis*).
- In **verruous epidermal nevus**, histology shows **hyperkeratosis, papillomatosis** and **vacuolization of the cells in the stratum spinosum and granulosum** with keratohyalin granules.
- **Botryomycosis** (pseudomycosis - NOT caused by fungus) is caused by many **bacteria** like *Pseudomonas*, *E. coli*, *Actinobacillus* and *Staph aureus*.
- Substance common to **skin, hair and nails** is **keratin**.
- Constituents of **sebum** = Glycerides + free fatty acids (57%); wax esters, squalene, cholesterol esters and cholesterol.
- **Paracetamol** causes **phototoxic** reactions.
- **Gianotti Crosti syndrome:** A **papular acrodermatitis of childhood**; a **self-limited childhood exanthema**; a/w **hepatitis B virus** and other viruses.
- **Adamson's fringe:** It is located at upper margin of hair bulb where nucleated hair shaft cornified completely and gets converted to hard anucleated keratin.
- **Mast cell degranulation markers:**
 - **Specific markers:** Tryptase (Alpha tryptase in systemic mastocytosis and Beta tryptase in recent anaphylaxis) and CD117.
 - **Others:** Chymase; Beta-hexosaminidase; Histamine; Heparin, Chondroitin Sulphate E; TNF, PGD2, LTC4.

MORE ONE-LINERS

- **Indurated seminal vesicle** seen in **tubercular epididymitis**.
- **Black tongue** with hypertrophy of papillae maybe seen with **imbalance of bacterial flora** due to antibiotic use. Black tongue with hypertrophy of papillae may be seen with **cocaine smoking; tobacco abuse; lansoprazole; chewing bismuth; methyl dopa; minocycline** and **hydroxychloroquine**.
- **Ash leaf macules** are the **first** skin sign of **tuberous sclerosis**.
- **Orf (Ecthyma Contagiosum):** (by **parapox virus**, a/w exposure to infected **sheep**); **Milker's nodules** (by **paravaccinia** found in **cows**).
- **Salt and Pepper** skin is seen in **Scleroderma**.
- Wavelength of **CO₂ laser** is **10,600 nm**.
- **Acute infectious purpura fulminans (AIPF):** The two MC causes of AIPF are **meningococcus** and **varicella** precipitated by bacterial **endotoxin**.
- **Torre syndrome:** Multiple sebaceous adenomas.
- **Dowling Degos disease (Dark Dot disease, AD):** **Reticulate hyperpigmentation** of flexures, dark comedo like lesions and **pitted acneiform scars** with childhood onset.
- **Kamino bodies:** Eosinophilic globules seen in basal layer of epidermis above tips of dermal papillae; seen in **spitz nevi**, melanomas and ordinary nevi.
- **Benign sweat gland tumors:** Syringoma, cylindroma, nodular hidradenoma, eccrine poroma.
- **Benign hair follicle tumors:** *Trichoepithelioma*, *Pilomatrixoma*, *Trichofolliculoma*.

CHAPTER

27

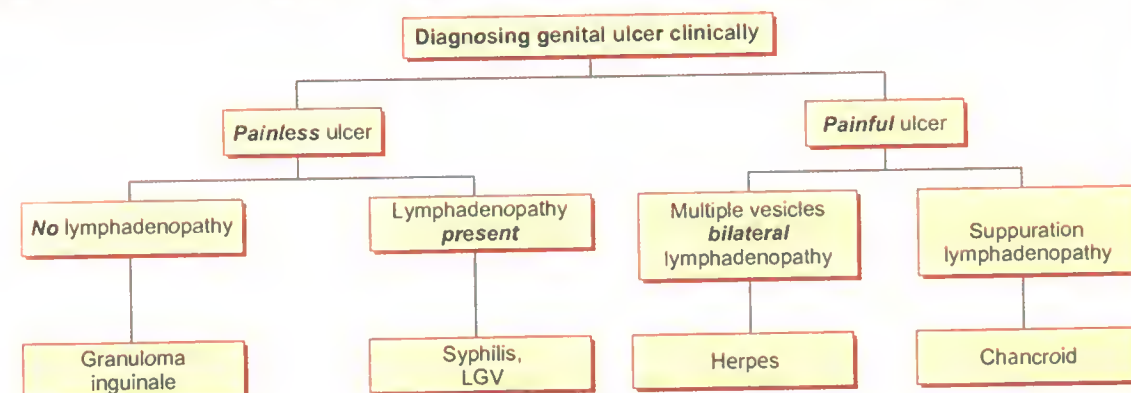
Venereology

SEXUALLY TRANSMISSIBLE MICROORGANISMS (PREDOMINANT ROUTE)

Bacteria	Viruses	Others
<ul style="list-style-type: none"> • <i>Neisseria gonorrhoeae</i> • <i>Treponema pallidum</i> • <i>Haemophilus ducreyi</i> • <i>Klebsiella (Calymmatobacterium) granulomatis</i> • <i>Chlamydia trachomatis</i> • <i>Ureaplasma urealyticum</i> • <i>Mycoplasma genitalium</i> 	<ul style="list-style-type: none"> • HIV (types 1 and 2) • Herpes simplex virus type 2 (HSV 2) • Human papilloma virus (HPV) • Human T-cell lymphotropic virus type I (HTLV1) • Hepatitis B virus (HBV) • Molluscum contagiosum virus 	<ul style="list-style-type: none"> • <i>Trichomonas vaginalis</i> • <i>Phthirus pubis</i>

D/D OF COMMON STDs

Chancroid (soft sore)	Granuloma Inguinale (Donovanosis)	Lymphogranuloma Venereum (LGV)
Etiology		
<ul style="list-style-type: none"> • Gram-negative bacillus <i>Haemophilus ducreyi</i>; "school of red fish" appearance; ("DuCREY = its painful, U Du CRY !!") 	<ul style="list-style-type: none"> • <i>Calymmatobacterium granulomatis</i>, a pleomorphic, gram-negative rod. • First described by McLeod in India; later Donovan described intracellular (Donovan) bodies-under Wright-Giemsa stain, the bipolar condensation of chromatin gives a "safety pin" appearance; seen in large mononuclear (Pond) cells. 	<ul style="list-style-type: none"> • <i>C. trachomatis</i> strains of the L1, L2 and L3 serotypes, L2 is MC. • Smears of pus from lesions may show the elementary bodies (MiyagaVa's granulacarpuscles). • Frei's intradermal test using lygranum antigen has also been used. • The classical lesion of this disease is the stellate abscess
Clinically		
<ul style="list-style-type: none"> • Incubation period = 4 to 7 days. • Acute, multiple (due to autoinoculation), irregular, nonindurated (hence 'soft sore/chancre'), very painful, sharply circumscribed foul smelling ulcers with undermined edges and granulation tissue at the base. Inguinal lymph nodes usually unilaterally, become tender, matted, unilaculated, suppurative, fluctuant and may rupture through the skin 	<ul style="list-style-type: none"> • Incubation period = 8 days to 12 weeks; • Painless elevated ulcer with beefy-red, friable, granulation tissue with rolled edges; usually occurs on the glans penis/vulva or vagina; subcutaneous granulomas may develop in the inguinal region called 'pseudo-buboes' ('pseudo'-becoz NO true regional lymphadenopathy); ("Pseudobubo-Granuloma Inguinale = PGI = 'Pain Gayab Isme !!"). 	<ul style="list-style-type: none"> • Incubation period = 1 to 4 weeks • Primary stage: Small painless vesicle/papule, asymptomatic and heals soon without scarring-goes unnoticed. • Secondary stage: Inguinal syndrome-MC in heterosexual men. About 2 to 6 weeks later, a unilateral painful, inguinal lymphadenopathy - "sign of the Groove (of Greenblatt)"
Treatment		
<ul style="list-style-type: none"> • (buboes); phagedenic ulceration, phimosis, urethral fistulae and urethral stricture are the other complications; Obsolete skin test = 'Ita test' • Single dose: Azithromycin or Ceftriaxone; Needle aspiration through normal skin (to prevent fistula formation) 	<ul style="list-style-type: none"> • 3 weeks-Doxycycline or azithromycin 	<ul style="list-style-type: none"> • Tertiary stage: Genitoretal syndrome - Proctocolitis, perirectal abscess, fistulas, strictures, and lymphorrhois; end result can be esthiomene (genital elephantiasis). • Doxycycline is DOC



Genital Herpes

- **Genital Herpes (Herpes Progenitalis)** is caused by **HSV 2**
- Multiple **painful vesicles** and maybe a/w **bilateral tender lymphadenopathy** but **NO** induration
- Treat with acyclovir, valacyclovir, or famciclovir.

SYPHILIS ('THE GREAT IMITATOR')

Etiology

- **Schaudinn and Hoffman** discovered *T.pallidum* in 1928.
- *T.pallidum* is a **spirochete**, (trepos, meaning to turn, and nema meaning thread); Its morphology/motility can be seen under the **dark ground microscope**.
- **Six endoflagella** wind around the cell body and may be the elements responsible for active motility. During motility secondary curves appear and disappear in succession, but the primary spirals are unchanged.
- Stains for *T.pallidum*: stains **light rose red with Giemsa stains**; **silver** impregnation methods also used; **Fontanas method** is for staining films and **Levaditi's** for tissue sections.
- ***Treponema pallidum*** may survive in refrigerated blood for 3 days; may remain viable for several years if frozen below 78°C.



Fig. 27.1: Treponema pallida

Primary Syphilis

- ▶ **Hunterian (Hard) chancre** occurs on the penis or scrotum of men and on the vulva, cervix or perineum of women.
- ▶ It is a **highly infectious, single, painless, ulcerated lesion, is indurated** and has characteristic cartilaginous consistency on palpation of the edge and base of the ulcer.
- ▶ **Regional lymph nodes are bilaterally enlarged, firm, nonsuppurative and painless (non-tender)**; this chancre generally **heals within 4–8 weeks**.

Secondary Syphilis

- Presents with **non-pruritic skin papules (NOT vesicular AND it involves palms and soles)** within 2–10 weeks after the primary chancre; **Generalized non-tender lymphadenopathy is present**.
- Constitutional Symptoms: Malaise, headache, anorexia, nausea, aching pains in the bones and fatigue are often present, as well as fever and neck stiffness.

Skin affection in secondary syphilis

- ▶ **Macular roseola**: Rose colored spots on the chest and upper arms.
- ▶ Hair follicles involvement → patchy alopecia; **"moth eaten alopecia"** and a diffuse alopecia.
- ▶ **Condyloma lata**: Highly infectious papules in perianal region.
- ▶ **Framboesiform syphilide**: Large papules crusted with dry serum.
- ▶ **Corymbose syphilide**: Large papule surrounded by small papules.

- Less Common Complications of Secondary Syphilis:
 - ▶ **Hepatitis** (↑↑ serum alkaline phosphatase, some hepatocellular damage and no cholestasis).
 - ▶ **Nephropathy** (acute nephrotic syndrome).
 - ▶ GI involvement (hypertrophic gastritis, patchy proctitis), arthritis and periostitis.

- ▶ Ocular findings: **Interstitial keratitis; granulomatous uveitis; neuroretinitis; Argyll Robertson pupil; optic neuritis, ocular motor palsies** of the third and sixth cranial nerves.

Latent Syphilis

- **Positive treponemal and specific antibody tests for syphilis**, together with a **normal CSF examination** and the **absence of clinical manifestations of syphilis**, indicate a diagnosis of latent syphilis.
- **Early latent syphilis** encompasses the **first year after infection**, while late latent syphilis begins 1 year or longer after infection in the untreated patient.

Tertiary Syphilis

- This usually develops within 3–10 years of primary infection; there are **gummas** (granulomas occurring in the skin, mucosa, bone, joints, rarely viscera, e.g. lung, testis).
- Cutaneous gummas tend to heal at the center leaving thin, atrophic **'tissue paper' scar**.
- Mucosal gummas are painless, localized swellings which break down to form characteristic **'punched out' ulcers** with **'wash leather' slough**.
- **Bony gummas** are usually seen in the tibia and cranial bones, resulting in osteitis and osteomyelitis.

Quaternary Syphilis

- Very rare and occurs in about 10% of untreated syphilitics-affects **heart and CNS**.
- **Cardiovascular syphilis**: aortitis (**tambour quality** to the second heart sound; **"tree bark"** appearance of ascending aorta), ascending aortic saccular aneurysm ± aortic regurgitation; linear calcification of ascending aorta; left ventricular hypertrophy (**cor bovinum**).

Syphilis of the CNS

- ▶ **Neurosypilis**: Features are cranial nerve palsies, seizures and stroke.
- ▶ **General paresis of insane (GPI)**: Features correspond to the mnemonic **PARESES**: **P**ersonality, **A**ffect, **R**eflexes (hyperactive), **E**ye (e.g. Argyll Robertson pupils), **S**ensorium (illusions, delusions, hallucinations), **I**ntellect (a decrease in the recent memory and capacity for orientation, calculations, judgment and insight) and **S**peech.
- ▶ **Tabes dorsalis**: **Locomotor ataxia**, numb legs, chest, and bridge of nose, lightning pains, gastric crises, reflex loss, flexor plantars, Charcot's joints, Argyll Robertson pupil.— due to degeneration of dorsal roots of **spinal cord**.

Dark Field Examination

- Useful in primary and secondary syphilis and in cases of congenital syphilis with superficial lesions. The **transudate from the lesions is examined under a dark ground microscope**; identification of a **single motile organism** (slender spiral structure and slow movement) by a trained observer is **sufficient for diagnosis**.
- A single negative examination does not exclude the possibility of syphilis, since **at least 10⁴ treponemes per microliter of transudate must be present** to be seen.
- Ideally, the dark field examination should be **repeated on three successive days** before being considered negative.

Serologic Tests for Syphilis

Nontreponemal tests	Treponemal tests
<ul style="list-style-type: none"> • Detects anti-cardiolipin 'reaginic' antibody-indicates active disease and become -ve after treatment • Used for screening and diagnosis and monitoring response to treatment • VDRL (Venereal Disease Research Laboratory test, slide flocculation test)-MC used test for syphilis. • RPR (Rapid Plasma Reagin test) • (Wassermann reaction-complement fixation test and Kahn test-tube flocculation test NOT routinely used now) 	<ul style="list-style-type: none"> • Detects Specific antibody against T. pallidum—+ve during primary disease and remains so despite treatment • Confirmatory test-whether a +ve non-treponemal test is a false-+ve result or is truly indicative of syphilis • <i>T. pallidum</i> particle agglutination (TPPA) test (first choice-CMDT 2014. Pg 1419) and FTA-ABS (most sensitive test) • Both FTA-ABS and TPPA are more sensitive than TPHA (<i>T. pallidum</i> haemagglutination test) • TPI (<i>T. pallidum</i> immobilization test): is the most specific test; (but NOT used routinely)

Special Notes

- Both types of tests are reactive in persons with any treponemal infection, including **yaws, pinta and endemic syphilis**.
- **False-positive VDRL**: Seen in **connective tissue diseases, infectious mononucleosis, malaria, febrile diseases, leprosy, intravenous drug use, infective endocarditis, old age, HCV and HIV infection, and pregnancy**.

- In **primary syphilis**, **treponemal tests** are more sensitive than VDRL/RPR.
- In **secondary syphilis**, treponemes are seen in the lesions and both types of antibody tests are positive.
- Fewer than 1% of patients with high titers have a nontreponemal test that is nonreactive or weakly reactive with undiluted serum but is reactive with diluted serum—the **prozone phenomenon**.
- In **late syphilis**, **organisms may no longer be seen**, but both types of antibody test usually remain positive (BUT VDRL and RPR tests may wane).
- In **neurosyphilis**, CSF antibody tests are positive.
- If **HIV positive**, serology may be **negative** during syphilis reactivation.
- **Efficacy of treatment** should be assessed by clinical evaluation and **monitoring of the quantitative VDRL or RPR titer** for a fourfold decline (e.g. from 1:32 to 1:8).
- **Chancre redux** is a feature of **early relapsing syphilis**.
- **Testis is involved earlier** in epididymitis in syphilis.
- **Vesicular rash** is seen in **congenital syphilis**.

Treatment

- **Penicillin** is **The DOC** for *T. pallidum* even after 60 years !!

Stage of syphilis	Without penicillin allergy	With penicillin allergy
Primary syphilis and Early latent Syphilis	Benzathine Penicillin G (single dose of 2.4 mU IM) CSF abnormal. Treat as neurosyphilis	Tetracycline or doxycycline
Late latent, cardiovascular, or benign tertiary	Benzathine Penicillin G (2.4 mU IM weekly for 3 weeks)	Tetracycline or doxycycline
Neurosyphilis	Aqueous crystalline penicillin G IV for 10–14 days or Aqueous procaine penicillin G plus oral probenecid both for 10–14 days	Desensitization and treatment with penicillin
Syphilis in pregnancy	According to stage	Desensitization and treatment with penicillin

Note

- **Jarisch-herxheimer reaction**: An **intensification of symptoms** because of the **release of the antigenic protein when the spirochete is destroyed by penicillin**. **MC in secondary syphilis**; most dangerous in tertiary. Consider steroid cover.
- For **congenital syphilis**—see under Pediatrics chapter (Pg 695).

ENDEMIC TREPONEMATOSES

- Endemic (**non-venereal**) treponematoses occur in less developed areas of the world.
- NO serologic or microbiologic test can differentiate endemic treponematoses from venereal syphilis or each other, since they are caused by treponemes with no demonstrated significant morphologic or genetic differences from *T. pallidum*.
- Diagnosis is **clinical**.
- All results in **disfiguring lesions of skin**.
- **Endemic syphilis (Bejel)** *T. pallidum*; affects skin, bones and mucous membranes
- **Yaws (Pian, framboesia)** *T. pertenue*; affects skin and bones (**periostitis**)
- **Pinta** *T. carateum*; Affects skin alone (non-destructive)

URETHRITIS

Urethritis in Men

- **MC cause** = Chlamydia trachomatis
- **Gram stained smear** of urethral exudate = **98% sensitive for gonococci** (gram-negative diplococci)
- Treatment: Gonorrhea (Rx with **ceftriaxone 250 mg IM single dose**); Chlamydia trachomatis (**azithromycin or doxycycline**).

Urethritis and the Urethral Syndrome in Women

- Causes: *C. trachomatis* (**MC cause of non-gonococcal urethritis NGU**), *N. gonorrhoeae*, and HSV; characterized by **"internal" dysuria** (usually without urinary urgency or frequency), pyuria, and an absence of Escherichia coli and other uropathogens at counts of 100/ml in urine. **NAAT** (Nucleic Acid Amplification Test) are sensitive and specific for gonorrhea and *C. trachomatis*.
- **External dysuria** = Dysuria being caused by painful contact of urine with the inflamed or ulcerated labia or introitus; a/w vulvar herpes or candidiasis (and perhaps with trichomoniasis).

Epididymitis

- **Acute epididymitis**, usually unilateral, produces **pain, swelling, and tenderness of the epididymis**.
- **MC cause** in **sexually active men** under age 35 = *C. trachomatis*.
- **MC cause** in older men or following **urinary tract instrumentation** = urinary pathogens.
- Treatment: **Ceftriaxone followed by doxycycline**.
- D/D is **Torsion**: A surgical emergency, usually occurs in the second or third decade of life and produces a sudden onset of pain, elevation of the testicle within the scrotal sac, rotation of the epididymis from a posterior to an anterior position, and absence of blood flow on Doppler examination or 99mTc scan.

PSM ASPECTS OF STDs

Case detection in sexually transmitted diseases (STDs) may be made by:

- **Screening** Testing of apparently healthy volunteers from the general population for the early detection of disease.
High priority is given to **people of special groups** viz. pregnant women, blood donor, industrial worker, army, police, refugees, prostitutes, etc.

Contd...

STD Color-Coded Kits

Kit	Color	Syndrome	Content
1	Grey	Urethral/Anorectal/Cervical discharge	Azithromycin, Cefixime
2	Green	Vaginal discharge	Secnidazole, fluconazole
3	White	Genito-ulcerative disease (Non-herpetic)	Azithromycin, Benzathine penicillin
4	Blue	Genito-ulcerative disease (Non-herpetic)	Azithromycin, Doxycycline
5	Red	Genito ulcerative disease (Herpetic)	Acyclovir
6	Yellow	Low abdominal pain	Cefixime, Metronidazole, Doxycycline
7	Black	Inguinal bubo	Azithromycin, Doxycycline

Suraksha Clinic

- Chain of STD clinics to provide reproductive and sexual health services
- Established by National AIDS control Program, NACO

Contd

- **Contact tracing** A technique by which the sexual partners of diagnosed patients are identified, located, investigated and treated
Is one of the best methods to controlling the spread of infection
Is relatively expensive (in low prevalence)
Key to success is patient himself (who must disclose all sexual contacts voluntarily)
- **Cluster testing** Here the patients are asked to **name other persons of either sex who move in the same socio-sexual environment**. These persons are then screened (blood testing).

Syndromic Management

- Since 1990 WHO has recommended **syndromic management of STDs** in patients presenting with consistently recognized signs and symptoms of STDs.
- See **Park's textbook** for the flowcharts on syndromic management of STDs.

Syndromic approach is applied to the following signs and symptoms of STDs

- › **Urethral discharge**
- › **Genital ulcer**
- › **Vaginal discharge**
- › **Inguinal bubo** (enlarged and/or painful inguinal lymph nodes)

- Purpose: Control of STI/RTIs viz., HIV, Syphilis, Gonorrhea, Herpes, Chlamydia, Genital warts
- Facilities: Blood sample testing; Counselling; Syndromic case management (RTI/STI/RPR kits)

Psychiatry

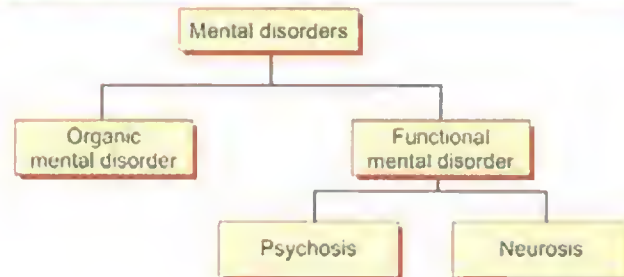
IMPORTANT NAMES IN PSYCHIATRY

Name	Contribution
Reil, Johann	Coined 'Psychiatry' Founded the first psychiatric journal
Freud, Sigmund	Founder of psychoanalysis Coined - 'Free association', 'Oedipus'; 'Penis envy', 'Id, Ego and Superego' Wrote book 'Interpretation of dreams' in 1900 Cocaine in psychiatry Psychodynamic theory
Philippe Pinel	Moral and Humane treatment of mentally ill
Alfred Adler	Coined: 'Inferiority complex'; Founder of school of individual psychology
Pavlov, Ivan	Coined - 'Classical conditioning' Animal studies on controlled reflexes
Piaget, Jean	Stages of cognitive development
Jung, Carl	Founder of the school of analytical psychology Coined 'Introvert/Extrovert'; 'Electra complex'
Alfred Binet	Gave the first formal scale of intelligence
Beck AT	Cognitive therapy; Cognitive theory of depression
Kubler Ross	5 stages of grief in dealing with Death
Erik Erikson	Divided life cycle into 8 stages
Bleuler, Eugen	Coined: 'Schizophrenia'; 'Ambivalence' Described cardinal symptoms (4A's) of SZ
Dendy, Walter	Coined: 'Psychotherapy'
Emil Kraepelin	'Dementia praecox'
Karl Kahlbaum	Coined: 'Catatonia'
Franz Alexander	Father of psychosomatic medicine
Jones, Maxwell	Therapeutic community
Mesmer, Anton	Coined 'Animal magnetism'

CLASSIFICATION

- The simplest way to describe a psychiatric disorder is as a disturbance of
 - > **Cognition** (i.e. thought), or
 - > **Conation** (i.e. action), or
 - > **Affect** (i.e. feeling) or any disequilibrium between the three.
- There are 2 major classifications in psychiatry.
 - ICD-10** (International Classification of Diseases-X revision, 1992) is WHO's classification for all diseases, injuries and death; **chapter F** classifies psychiatric disorders, F(00-99); F20-29 - Schizophrenia; F30-39 - Mood disorders.
 - The American Psychiatric Association (APA) published **DSM-5** in 2013. The major changes in DSM-V are mentioned at the end of this chapter. **ICD-11** will be finalized in 2018.
 - DSM-IV** (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), codes diagnoses of specific psychiatric illnesses along a multi-axial (5 axes) system as below:
 - Axis I—Clinical psychiatric disorders.
 - Axis II—Personality disorder and mental retardation.
 - Axis III—Physical disorders and general medical conditions.
 - Axis IV—Psychosocial and environmental problems.
 - Axis V—Global assessment of functioning.

MENTAL DISORDERS



Organic Mental Disorder

Disease/Disorder occurring due to **underlying disease of the brain**

Acute onset

Affects in **old age**

Consciousness is **impaired**

Prominent **visual** hallucinations

Neurological deficit **present**

Ex: **Delirium** (MC organic mental disorder); Dementia; Wernicke Korsakoff's psychosis

Functional Mental Disorder

Disease/disorder with **NO** such basis; Further classified into two types (**psychosis and neurosis**) as below

Gradual onset

Affects in **young age**

Consciousness is **preserved**

Mainly **auditory** hallucinations

Neurological deficit **absent**

Ex: **Schizophrenia**; **bipolar mood disorder**, etc.

Psychosis

Insight - Absent (i.e. awareness and understanding of the disease by the patient, is absent)

Judgment and reality testing - Impaired

Delusions and hallucinations - always present

Personality and behavior - Impaired

Ex: Mania; Schizophrenia

Neurosis

Insight - Preserved

Judgment and reality testing - Preserved

Delusions and hallucinations - absent

Personality and behaviour - Preserved

Ex: OCD, PTSD, Panic disorder, GAD, etc..

MENTAL STATUS EXAMINATION

Interview - Look for -

- Appearance
- Motor behavior
- Verbal output (speech)
- Mood and Affect
- Thoughts
- Perception

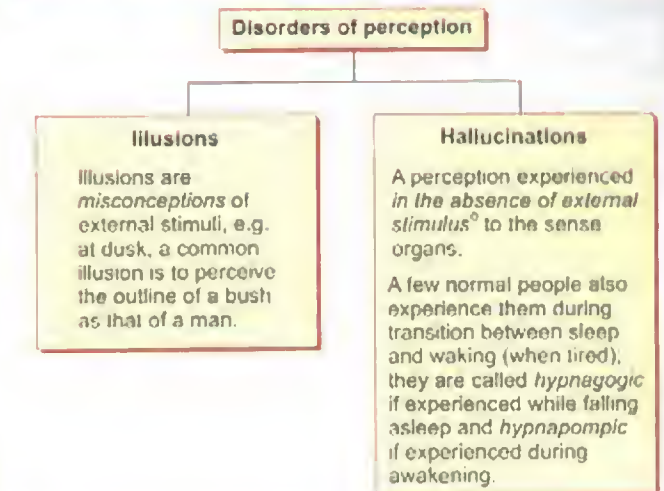
Mental status - Test for -

- Attention and concentration
- Memory
- Language construction
- Calculation skills
- Abstraction
- Insight and judgment
- Praxis

EXTRA EDGE

- Abstraction** = (tell 3 similarities between car and bike; bird and aeroplane; medicine and dentistry; **proverb** interpretation - What is the meaning of 'Early bird catches the worm?')
- Judgment** = (ability to take sound decisions and act on them, e.g. What will you do if your house is on fire?)
- Food preference** (food history) is NOT of significance in psychiatric history taking.
- Psychiatrist is NOT posted in **PHC** (primary health center).

DISORDERS OF PERCEPTION



According to Complexity

- **Elementary hallucinations** - bangs, whistles, flashes of light.
- **Complex hallucinations** - hearing voices or music, or seeing faces and scenes.

According to Sensory Modality

- **Auditory hallucinations:**
 - > Voices **addressing the patient** (**second-person** hallucinations) and voices talking to one another **referring** to the patient (**third person** hallucinations) seen **commonly in schizophrenia**.
 - > Sometimes voices seem to anticipate what the patient thinks a few moments later, or speak his own thoughts as he speaks them (**Gedankenlautwerden**), or repeat his thoughts immediately after he has thought of them (**echo de la pensee**).
- **Visual hallucinations:**
 - > These may be **unformed** (photopsia/flashes) or **formed** (objects, people, etc.); **common in organic mental disorders (delirium)** also seen in **temporal lobe lesions**.
 - > **Extracampine**: hallucinations beyond the possible sensory field, e.g. 'seeing' somebody standing behind you (located outside the field of vision) is a visual extracampine hallucination.
- **Olfactory and gustatory hallucinations:**
 - > Unpleasant smell or tastes; may suggest severe **depressive disorders, schizophrenia, temporal lobe epilepsy, irritation of the olfactory bulb** by a tumor

- **Tactile (haptic) hallucinations:**

- Experienced as insects crawling on the body or under the skin; occurs with **cocaine abuse (formication of Magnan's bugs)**, **amphetamine abuse**, **delirium tremens**, **opioid withdrawal**, and occasionally in schizophrenics.

- **Autoscopic hallucination:**

- It is the experience of *seeing one's own body projected into space*, usually in front of oneself for short periods. This experience may convince the person that he has a double (**doppelganger**); a rare phenomenon encountered mainly in a small minority of patients with **temporal lobe epilepsy**.

- **Hallucinations in relation to time of sleep**

- **Hypnagogic** (occur while **GOing** to sleep) i.e. *starting to sleep*
- **Hypnopompic** (just as the patient wakes up)

DISORDERS OF THOUGHT**Healthy Thinking**

Healthy thinking has three components (Schneider)

1. Constancy
2. Organization
3. Continuity

Disorders of the Stream of Thought

- **Pressure of thought** (ideas arise in unusual variety and abundance and pass through the mind rapidly), **poverty of thought** (only few thoughts) and **thought blocking** (interruption of thought); all these may be experienced in **schizophrenia**.

Disorders of the Form of Thought

- **Flight of ideas** (patients thoughts and conversation move quickly from one topic to another); characteristic of **mania**.
- **Perseveration** means *persistent repetition of words beyond their relevance*; occurs in **dementia** and **schizophrenia**.
- **Neologisms**: They are newly formed words or phrases whose derivation cannot be understood; MC in **schizophrenia**.
- **Word approximations or paraphasias**: here the derivation of the word can be understood (e.g. describing stomach as a 'food vessel').
- **Loosening of associations** (see box below).

Loosening of associations

This denotes a loss of the normal structure of thinking; occurs MC in **schizophrenia**. It may take any one of the below forms:

- **'Knights move' or derailment**: refers to a transition from one topic to another either between sentences or in mid-sentence with no logical relationships between the two topics.
- **Word salad**: an extreme form of derailment where the grammatical structure of speech is also affected.
- **Verbigeration** refers to senseless repetition of same words or phrases over and over again.
- **Vorbeireden** (German, for talking past the point—*parologia*), the subject seems always about to get near to the matter in hand but quite never reaches it.

Abnormal Thoughts (Delusions)

- **Delusion** is a *false belief* held on inadequate grounds, is not affected by evidence to the contrary, and is not in keeping with the patients sociocultural and economic background.
- **Nihilistic delusions**
 - **Nihilistic** is the root of the word '**annihilate**' and means *destruction or death*.
 - People experiencing nihilistic delusions believe things like *they are decomposing, their bodies do not work, their internal organs are rotten or solidifying or even that they are actually dead!* (e.g. **Cotard's syndrome** in **severe depression**)
- **Delusions of reference**
 - Seen in **schizophrenia**
 - These delusions are concerned with ideas that objects, events or people, have a personal significance to the patient; e.g. a radio play about homosexuals is thought to have been broadcast in order to tell the patient that everyone knows he is a homosexual.
- **Delusions of grandeur**
 - Occur in **mania** and **schizophrenia**
 - Beliefs of exaggerated self-importance. Patient may think himself to be *a king and wealthy*
- **Delusions of guilt**
 - Found most often in **depressive illness** (also delusions of worthlessness)
- **Delusions of control**
 - Strongly suggest **schizophrenia**; (e.g. the patient believes that his thoughts are controlled by an outside agency)
- **Induced delusional disorder**

- This is characterized by *sharing of delusions* between two persons (**folie a deux**) or occasionally more persons (**folie a trois**, **folie a quatrae**, **folie a familie**) who usually have closely knit **emotional bond**. Treatment is geographical, and **separation** works very well.

- **Ex:** A 20-year-old woman whose psychotic mother believes that aliens are coming to kidnap her now begins to believe the same thing. The belief disappears when her mother moves to another city.

Loosening of associations

- **Delusions of jealousy**

- MC in **men**
- When the content of delusion is mainly *jealousy (infidelity) involving the spouse*, it is called **Othello's syndrome** (conjugal paranoia, morbid jealousy). Morbid jealousy is more common among **alcoholics**.

- **Sexual or erotic delusions**

- Rare and MC in **women**; seen in **bipolar disorder**
- A woman believes that a man, who is inaccessible, of a higher social status and, to whom she has never spoken, loves her; a prominent feature of **erotomania (de Clerambault's syndrome)**

- **Capgras syndrome: Delusion of doubles**

- MC in **women**, MC in **paranoid schizophrenia**, also seen in delusional disorders, Lewy body dementia.
- **Illusion des sosies**—The person sees a *familiar person as a stranger who is imposing as the familiar person*.
- **Illusion de Fregoli**—The person falsely identifies strangers as familiar persons.

NEUROCOGNITIVE DISORDERS

Also known as **organic mental disorders** and includes **delirium**, **dementia** and **amnesia** as below.

Delirium (Acute Confusional State)

Patient Example: One week after a myocardial infarction, a 58-year-old man with no history of psychiatric illness becomes agitated and reports seeing strange animals in his room.

Cardinal Features

- MC organic disorder seen in clinical practice: **Impaired conscious level** with **acute onset** (over hours or days); **Disorientation in time (MC)** and in place with a **decreased attention span** and **distractibility**; Fluctuation of symptoms, worse in the evening and night (**sun**

downing); **disturbance of sleep-wake cycle** with insomnia at night and daytime drowsiness.

- Perceptual disturbances like illusions, **hallucinations (MC visual)** are common; motor activity may be increased but is usually purposeless—**asterisks**, **myoclonus**, **carphologia/floccillation** (*picking at bed clothes*).
- **Thinking** is slow and muddled; ideas of reference and delusions (often persecutory) are common; **Mood disturbances** – lability, apathy, depression irritability; **Autonomic dysfunction**: sweating, tachycardia, pupillary dilatation; **Memory** – **impaired registration**, retention and recall of recent memory with relatively intact remote memory; **Insight is impaired**; EEG generalized **slowing**.

Etiology

CNS illness (meningitis, head trauma); systemic illness (e.g. liver, kidney, cardiovascular or lung disease); drug abuse (e.g. alcohol, sedatives, phencyclidine); drug withdrawal, particularly from sedatives (e.g. alcohol, benzodiazepines, barbiturates).

Dementia (Major Neurocognitive Disorder)

Patient example: A 74-year-old retired accountant is alert, but shows noticeable memory disturbance and does not know what day it is, nor can he precisely identify the woman next to him (his daughter). He has been a good driver, but now has been involved in three minor car accidents in the past 2 months.

Cardinal Features

- Strongest risk factor is ↑ **age**; **Global deterioration** of higher mental functions in **clear consciousness** that is **progressive** (chronic) and (usually) **irreversible**; Impaired recent memory (in early stages) short and remote memory (in later stages); **Deterioration of personality** with a lack of personal care; **Impaired judgement** and **reasoning**; **Speech**: syntax errors (difficulty finding the right word), aphasia, mutism; **Thinking** is slow and muddled, delusions, perseveration. No insight; Illusions, **hallucinations (MC visual)** are uncommon.
- All the above features *interfere with daily living skills*.
- Montreal Cognitive Assessment (**MoCA**), Mini Mental State Examination (**MMSE**) test are used.

Various Types of Dementias

- **Alzheimer's dementia:** **MC cause** of dementia – see below.
- **Vascular dementia (Multi infarct dementia):** essentially multiple small strokes. Usually evidence of vascular pathology (BP, past strokes), onset sometimes sudden and deterioration often **stepwise**.
- **Frontotemporal dementias** including Pick's disease: disproportionately **early personality changes** (apathy, hyperorality) and relative intellectual sparing; (drawing is spared)
- **Normal pressure hydrocephalus:** (dilation of ventricles without signs of intracranial pressure, due possibly to partial obstruction of CSF flow from subarachnoid space), **incontinence** early in **dementia** and **gait dyspraxia**.
- **Lewy body dementia:** Characterised by Lewy bodies in brainstem and neocortex, and a fluctuating but persisting cognitive impairment, parkinsonism and hallucinations (Capgras syndrome); **alpha-synuclein** defect; (memory is spared).
- **Ameliorable/reversible causes:** Hypothyroidism, ↓ B12/folate; syphilis; thiamine deficiency (from alcohol abuse); operable cerebral tumor (e.g. parasagittal meningioma); subdural hematoma; CNS cysticercosis; NPH.

Alzheimer's Dementia

- **Risk factors:**
 - Old age
 - +ve Family history; Female gender
 - Diabetes; Down's syndrome
 - Head trauma.
 - Genetic risks
 - **Apolipoprotein E4** (Apo E4). Carrying one E4 allele increases the risk for AD by 2- to 3-fold, whereas two alleles increase the risk 16-fold
 - Abnormalities of chromosomes 1 (presenilin 2), 14 (presenilin 1) and 21 (APP); chromosome 19 (apoE4).
- **Pathology:**
 - **Entorhinal cortex** and **hippocampal** atrophy (**medial temporal lobe**) and **lateral temporal cortex**.
 - **Senile (beta-amyloid) plaques** and **neurofibrillary tangles** with **tau protein**
 - **Loss of cholinergic neurons in the nucleus basalis of Meynert**
 - **AB 42 amyloid in cerebral arterial walls**
 - **Biondi ring tangles** are found in **choroids plexus** of Alzheimer's disease and normal aging brain.
- **Pathogenesis:**
 - Reduction in brain levels of **choline acetyltransferase** (needed to synthesis acetylcholine); abnormal processing of amyloid precursor protein.

- **Decreased activity** of acetylcholine and norepinephrine, somatostatin, vasoactive intestinal peptide and corticotropin.
- **PET imaging** with radioligands like Pittsburgh Compound-B (PiB) and 18F-AV-45 appear to be reliable for detecting brain amyloid.

Treatment of Alzheimer's dementia

- **Donepezil, rivastigmine, galantamine** (inhibition of acetylcholinesterase, with a resulting increase in cerebral levels of acetylcholine);
- **Memantine** (acts by blocking overexcited N-methyl-D-aspartate (NMDA) channels).
- Due to hepatotoxicity, **tacrine** is NOT used now.

EXTRA EDGE

- Area of the brain **resistant** to neurofibrillary **tangles** is **lateral geniculate body**.
- **Newer drugs** tried in dementia include **Fasudil (Rho Kinase inhibitor)** which causes vasodilation, also used in subarachnoid hemorrhage) and **Vinpocetine (PDE-1, Phosphodiesterase -1 inhibitor)**.

Folstein Mini-Mental Status Examination (MMSE)

- **MMSE** is a **30-point test** of **cognitive function** and used to **follow the progression of dementia**; takes < **10 minutes** to complete. See below further.
- **Orientation** (Name: season/date/day/month/year OR Name: hospital/floor/town/state/country). Orientation is given the highest score of **10 points**.
- **Working memory** (e.g. spell '**world**' backwards) and **Episodic memory (3-word recall)**.
- **Registration:** Identify **three objects by name** and ask patient to repeat
- **Attention and calculation:** **Serial 7s; subtract** from 100 (e.g. 93-86-79-72-65)
- **Recall:** Recall the three objects presented earlier
- Language comprehension
 - Naming: **Name pencil and watch**
 - Repeat '**No ifs, ands, or buts**'
 - **Follow a 3-step command** (e.g. 'Take this paper, fold it in half, and place it on the table')
 - Write '**close your eyes**' and ask patient to obey written command
 - Ask patient to **write a sentence**
 - **Figure copying:** Ask patient to copy a design (e.g. intersecting pentagons).

Montreal Cognitive Assessment (MOCA)

The MOCA is also used to identify patients with dementia; it is superior to the MMSE mentioned above.

Cognitive domain	Items	Score
Visual-spatial or executive	Copy a cube; draw a clock; complete a trail-making task	5
Naming	Name three depicted animals	3
Attention	Recall 5 digits forward, 3 digits backward, maintain letter vigilance, subtract 7's serially	6
Language	Repeat two phrases; generate a list of words starting with a specific letter	3
Abstraction	Identify the similarity between nouns (train/bicycle; watch/ruler)	2
Delayed recall	Recall five words rehearsed twice previously (face, velvet, church, daisy, red)	5
Orientation	Identify the date, month, year, day and city	6
Total score		30

Cortical and Subcortical Dementia Compared

Feature	Cortical dementia	Subcortical dementia
Site of lesion	Cerebral Cortex ; frontal; temporal-parietal-occipital association area; hippocampus	Thalamus, basal ganglia; brainstem; cerebellum
Higher cortical symptoms	Aphasia, Apraxia, Agnosia (prosopagnosia-inability to recognize familiar faces also called face blindness); acalculia	No
Motor symptoms	No	Dysarthria, ataxia, rigidity, dystonic tremors
Memory	Both recall and recognition is impaired	Impaired recall , almost normal recognition
Mood	Almost normal	Significant depression and anxiety
Examples	Dementia due to <ul style="list-style-type: none"> • Alzheimer's • Frontotemporal dementia (including Pick's disease) • Vascular dementia • Diffuse Lewy body disease • Chronic subdural hematoma • Creutzfeldt Jakob disease (CJD) 	Dementia due to <ul style="list-style-type: none"> • Parkinson's disease • Huntington's disease • Multiple Sclerosis • HIV • Normal pressure hydrocephalus • Progressive supranuclear palsy • Chronic meningitis

Organic Amnestic Syndrome

Patient Example: An alert 68-year-old man with a superficially jovial affect has a 30-year history of alcoholism. He claims that he was recruited into the army in 2008.

Cardinal Features

- **Memory loss** occurs with little other cognitive impairment and a **normal level of consciousness**.
- Both **retrograde amnesia** (i.e. memory for past events, particularly the recent past— patient can recall events immediately after they occur, but cannot do so a few minutes or hours afterwards) and **anterograde amnesia** (i.e. inability to register new memories); the patient *may fabricate forgotten information to cover memory loss (confabulation)*.
- Primary cause is **thiamine deficiency** as a result of long-term **alcohol abuse (Korsakoff's syndrome/psychosis)**.
- **Amnestic changes** correlate to lesions in the **dorsal medial nucleus of the thalamus**.

Cognitive Errors

- **Selective Abstraction** (mental filter) (Ex: Dr Ram got MDRD seat in MAMC after getting 10th rank in AIPGE exam; however he is depressed and dwells on the fact that he could not get MDRD in AIIMS!, i.e. he draws a conclusion based on 'selected' negative evidence).
- **Arbitrary inference** (Ex: Mrs X sent a wedding gift to her friend's daughter. She has not yet received any acknowledgement of the gift; so Mrs X thinks 'They obviously think I have poor taste!' - i.e. coming to a conclusion without any facts to support it)
- **Overgeneralization**—(Absolutistic, all or none) thinking (Ex: Dr X submitted an article to the British Medical Journal and it was rejected. So Dr X now thinks 'No journal will ever accept any article that I write!' -i.e. a generalization based on one type of occurrence).
- **Dichotomous (all or nothing) thinking** (Ex: Dr. X submitted an article to the British Medical Journal and it was returned with the reviewers comments to make certain changes. Dr. X now thinks 'I am a bad writer!' instead of recognizing that revision is a common part of the medical publication process, i.e. he views situations in terms of all or nothing/good or bad - nothing intermediate).
- **Magnification** (Ex: Ms X is not invited to a cocktail party at her office mates' house and she feels that 'She doesn't like me!', i.e. exaggerating the negative significance of an event).
- **Minimization** (Mrs X is feeling lonely and asks her grandson Mr Y to come and visit, but Mr Y is going to

Delhi and can't come; however to cheer her up he calls 2-3 times from Delhi, but still Mrs X feels he doesn't care for her! - i.e. undervaluing the positive significance of an event).

- **Personalization** (Ex: Mr Lallu sells vacuum cleaners door to door, after giving a 1 hour demonstration to Mrs X—she says that she liked his demo BUT cannot buy the vacuum cleaner. So Mr Lallu feels that he is a worst salesman!; whereas Mrs X did not buy since her husband lost his job and they don't have enough money now - i.e. a person takes full responsibility for circumstances without considering any other factors that may have contributed to it).
- **Catastrophic thinking** (Ex: On the first day in her new job as secretary, Julei's Boss asks her to type a letter; she types it and places the print on his desk for his signature before going for lunch - but on returning she finds the typed letter on her desk with one typing error circled in red ink and she has to retype the letter - so she thinks 'Thats it; I am going to lose my job now!' - i.e. always thinking that the worst will happen to her).

SCHIZOPHRENIA (SZ)

Patient Example: A 24-year-old man has been involved in a fight with his roommate whom he accuses of inserting an electronic transmitter in his brain. For this reason he has changed roommates a number of times over the last 5 years. He dresses strangely, shows poor grooming, and seems preoccupied by 'people giving him instructions in his head'.

Introduction

Emil Krapelin differentiated the major psychiatric illnesses into two types: **Dementia praecox and manic-depressive psychoses.**

Two main people a/w Schizophrenia

- **Eugen Bleuler** renamed *dementia praecox* as **schizophrenia (mental spitting)** and described the cardinal symptoms (**4A's**) of SZ.
 - **Ambivalence** (inability to decide for or against)
 - **Autism** (withdrawal into self)
 - **Affect disturbances** (inappropriate affect)
 - **Association disturbances** (loose associations)
- **Kurt Schneider's first rank symptoms**
 - **Auditory hallucinations:** audible thoughts (thought echo); voices discussing the subject in third person; voices commenting on his action.
 - **Thought withdrawal, thought insertion, thought diffusion or broadcasting.**
 - **'Made' affect,** impulses or actions.
 - **Delusional perception.**
 - **Somatic passivity**

Specific Characteristics

- SZ is a **chronic** mental disorder characterized by *disturbed thought, behavior and speech* and an abnormal affect (i.e. flat, blunted or inappropriate).
- The patient often has a *strange appearance, shows poor grooming* and is **socially withdrawn**.
- **NO** disturbance of consciousness, memory, intelligence, attention and is oriented to time, place and person.

Prodromal Signs and Symptoms

- Before the psychotic episode, the patient often **avoids social activities and makes few friends**. He is usually quiet, passive or irritable. Patient may also have physical complaints and show **newfound interest in religion, philosophy and the occult**.
- **Disorders of perception**
 - **Hallucinations:** **Auditory hallucinations are MC.** **Third person hallucinations** are characteristic (e.g. the patient hears two different voices talking about her when she is alone in a room). Olfactory, gustatory, visual tactile and **cenesthetic/visceral** hallucinations ('burning' of brain; blood flow 'felt' in blood vessels); **anwesenheit** (presence of someone/something).

• **Disorders of thought content**

- **Delusions:** **Primary delusions**, hallucinations (*autochthonous, wahneinfall*) in **clear consciousness** are almost **pathognomonic of SZ**. They appear **suddenly, fully developed and strong**. Such delusions form around a 'delusional perception' as evidenced by the patient, who on seeing the traffic lights go green (the delusional perception) knew that he had been sent to rid his hometown of money-minded people!!!!

- **Delusions of persecution are MC** (e.g. patient believes that she is followed by spies who want to steal government secrets from her).
- Delusions of *reference* (e.g. patient believes that he is being discussed on a national television program).
- Delusions of *grandeur* (e.g. patient believes that he is the king of India).

• **Disorders of thought process**

- **Thought blocking:** Sudden stop in middle of a sentence (e.g. the patient suddenly stops talking, even though her lips are moving, and she seems to be concentrating on an inner stimulus).
- **Autistic thinking: Illogical thinking** (e.g. **Von Domarus law**—Lord Rama was born in India, I am born in India; So I am Lord Rama).
- **Impaired abstraction** (e.g. when asked what brought him to the hospital, the patient says 'a car')

- **Neologisms**—Inventing new words (with a conscious attempt at humor, e.g. calling a psychiatrist as a '*medicinal shrinkomat*!!') and word approximations or paraphasias.

Disorders of form of thought

- **Loosening of associations**—Ideas shift from one subject to another in an unrelated or partially related fashion (e.g. the patient begins to answer a question about her job and suddenly launches into a lecture on capitalism).
- **Echolalia** (repetition by the patients of words or phrases of the examiner - e.g. doctor asks 'Are you feeling sad?' Patient responds 'Are you feeling sad?');
- **Preservation** (repeating a thought over and over, e.g. the patient says, 'I am sane.... I am sane.... I am sane.... I am sane....');
- **Word salad**—Uttering unrelated combinations of words and phrases (e.g. the patient says 'I am not so utterly pious that I am anyway not going to break it').
- **Tangentiality**—Beginning a response in a logical fashion, but then getting further and further away from the point and **never returns** to the original topic (e.g. Patient says 'I will tell you about my headache, but first let me tell you about other things in my head like thoughts about God').
- **Circumstantiality**—Unnecessary details and irrelevant remarks cause a delay in getting to the point, but ultimately he gets to the point, unlike in tangentiality (e.g. When asked about the age of a persons mother at death, he starts talking about how too many accidents happen and how too many people die in various accidents and ultimately tells her age at death!)
- Clang associations: using rhyming words ('I am sad, bad, mad, glad')
- Mutism; poverty of speech; verbigeration, overinclusion, concreteness, and ambivalence.

• **Positive and negative symptoms**

- **Positive symptoms**—are characterized by *excessive function; positive symptoms include delusions, hallucinations, strange behavior, and talkativeness*. These **symptoms respond well** to treatment with antipsychotic agents.
- **Negative symptoms**—are characterized by decreased function; **negative symptoms include**—Affective flattening; Attention impairment; Avolition apathy (lack of initiative); Anhedonia (inability to experience pleasure); Asociality (social withdrawal) and Alogia (lack of speech output). **Negative symp-**

toms respond better to atypical antipsychotics like clozapine, olanzapine, quetiapine and risperidone.

Types 1 and 2 SZ (Crow, 1980)

Type 1 SZ (Reactive SZ)	Type 2 SZ (Process SZ)
<ul style="list-style-type: none">• Prominent positive symptoms• Acute onset• Good premorbid adjustment• Good treatment response• Intact cognition• Intact brain structure• Reversible neurochemical disturbance• Bizarre behavior	<ul style="list-style-type: none">• Prominent negative symptoms• Insidious onset• Poor premorbid adjustment• Poor treatment response• Impaired cognition• Structural brain abnormalities (ventricular enlargement)• Irreversible since pathology is based on neuronal loss

Catatonic SZ

- **Acute onset in teens** or early adult life.
- Dominated by **echolalia, echopraxia, spontaneous motor overactivity, waxy flexibility (flexibilitas cerea), negativism, mannerisms, constrained attitudes, automatic obedience; stupor; schnauzkrampf** (a grimace resembling pouting).
- **Mitgehen** ('anglepoise lamp sign') is **moving a limb in response to slight pressure on it, despite being told to resist the pressure!**
- **Catatonia** leading to death is called **acute lethal catatonia or pernicious catatonia.**
- **Best prognosis.**

Hebephrenic SZ (Disorganized SZ)

- **Insidious onset** early in life (second decade).
- Delusions and hallucinations are **fragmentary and changeable.**
- Inappropriate and fatuous affect with meaningless giggles and a self-satisfied smile; disinhibition; **silly, incoherent**, eccentric behavior; mirror gazing; grimacing and mannerisms; or inert and pathetic.
- Poor prognosis.

Simple SZ

- Insidious onset in second decade with **characteristic negative symptoms, drift down the social ladder and living shabbily and wandering aimlessly.**
- Delusions/hallucinations are usually absent.
- Poor prognosis.

More special types of SZ**Paranoid SZ**

- Delusions of **persecution**.
 - **Later age** of onset (*third or fourth decade*).
 - **Better preservation of personality** than other types.

Pseudoneurotic SZ

- Consisting of pananxiety, panneurosis, pansexuality

Late paraphrenia

- Common in **women, widows or spinsters**.

Oneroid SZ

- Consisting of **dream like states**

Van Gogh syndr.

- Dramatic **self mutilation** occurring in SZ

Propf SZ

- Is SZ occurring in the **mentally retarded** (IQ < 70)

Neurotransmitter Abnormalities

- Excessive **dopaminergic** activity ('**dopamine theory of SZ**'); elevated levels of homovanillic acid (metabolite of dopamine) maybe present.
- **Serotonin hyperactivity; Norepinephrine hyperactivity** (in **paranoid SZ**); **Gamma amino butyric acid (GABA)**.

Pathology

- **Lateral and third ventricle enlargement**, abnormal cerebral symmetry, and changes in brain density.
- Frontal lobe abnormalities (**hypofrontality**).

Etiology

- '**Downward drift**' hypothesis—Because patients with SZ tend to drift down the socioeconomic scale as result of their social deficits, they are often found in **lower socioeconomic** groups (e.g. homeless people).
- Schizophrenia is observed in ~**6.6%** of all first-degree relatives of an affected proband. If both parents are affected, the risk for **offspring is 40%**. The concordance rate for **monozygotic twins is 50%**, compared to more people with SZ are born in the **winter** months
- SZ begins in **late adolescence**.

Treatment of SZ**Drug treatment**

- Antipsychotics is the treatment of choice.
- **Traditional antipsychotics** like **haloperidol and chlorpromazine** work primarily by blocking central D₂ receptors. These agents are particularly effective against **positive symptoms**.

Contd...

Contd...

Drug treatment

- **Atypical antipsychotics** are effective against **negative symptoms**, e.g. Clozapine, a **D₄ receptor antagonist** that also acts on the serotonergic system; it decreases suicidal tendency; useful in 'resistant' schizophrenia (For further details about the drugs, see the section on Psychopharmacology).
- **Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)** study compared 'atypical' and 'typical' neuroleptic medications.

- **Psychosocial treatment:** Psychosocial treatment includes group psychotherapy and family therapy.
- **Electroconvulsive Therapy (ECT):** Indications include:
 - Catatonic stupor
 - Uncontrolled catatonic excitement
 - Acute exacerbation not controlled with drugs
- **Miscellaneous treatments:** Which have been used in the past, are **megavitamin therapy, dialysis, malaria therapy** and **insulin coma** therapy.

Prognosis

- Impairment is commonly **lifelong**.
- **Suicide** can occur in SZ due to **command hallucinations**, anhedonia, impulsive behavior, etc. Suicide is the **MC cause of premature death** in SZ.
- (**Clozapine** is the **ONLY antipsychotic** that has received **FDA approval** for the **treatment of recurring suicidal behavior** in patients with schizophrenia)
- **As individuals age, positive symptoms tend to attenuate** and some measure of social and occupational function may be regained.
- However, **marked variability in the course** and individual character of **symptoms is typical**.
- 'Negative' symptoms are associated with a poor long-term outcome and a poor response to drug treatment.

Favorable prognostic points	Poor prognostic points
Acute onset of illness	Gradual onset
Onset after 35 years of age (late onset)	Onset before 20 years of age (early onset)
Short duration (< 6 months)	Long duration of illness, over 2 years
Precipitated by obvious environmental or physical factors	Absence of precipitating factors
Good premorbid adjustment (social, sexual and work history)	Poor premorbid adjustment Withdrawn autistic behavior

Contd...

Contd...

Favorable prognostic points	Poor prognostic points
Presence of depression	Absence of depression
A pyknic (euryomorphic) physique (round and fat)	Marked leptomorphic physique (thin)
A H/O previous attacks from which the patient has made recovery	No remissions in 3 years Many relapses
Married	Single, divorced or widowed
Family history of mood disorders	Family h/o SZ Poor support systems
Good support systems	Negative symptoms H/o perinatal trauma and H/o asualliveness
Positive symptoms	High Expressed emotion (more criticism, hostility and emotional over-involvement) among family members is a risk factor for relapse

EXTRA EDGE

- **Velocardiofacial syndrome**, the MC known interstitial deletion found in humans (22q11.2 deletion), is a/w high rates of **SZ**.
- SZ is a/w increased risk of **stroke**.
- **PANSS** - Positive and Negative syndrome scale—used for measuring symptom severity of patient with SZ. It is widely used in the study of anti-psychotic therapy.

Diagnostic Criteria (as per DSM V)

- The **diagnostic criteria** for schizophrenia are:
 - Hallucinations
 - Delusions
 - Disorganized speech (derailment or incoherence)
 - Disorganized behavior
 - Negative symptoms.
- Out of the above five criteria, **two or more** should be present of which 1 should be either (a), (b) or (C).
- Duration of symptoms > **6 months** = '**Schizophrenia**'.
- Duration of symptoms is **1-6 months** = '**Schizophreniform disorder**'
- Duration of symptoms < **1 month** = '**Brief psychotic disorder**'
- The **DSM-IV subtypes** of schizophrenia (i.e. **paranoid, disorganized, catatonic**) have been **eliminated**.

EXTRA EDGE

- As per ICD-10 duration of symptoms > 1 month is called Schizophrenia; if it's for 15 days it is called 'Acute and Transient Psychotic disorder'.

MOOD DISORDERS

Unipolar	Bipolar	Etiologic
<ul style="list-style-type: none"> Major depressive disorder Dysthymic disorder 	<ul style="list-style-type: none"> Bipolar I disorder Bipolar II disorder Cyclothymic disorder 	<ul style="list-style-type: none"> Substance induced mood disorder Mood disorder due to general medical condition

Etiology

- Biologic causes: altered neurotransmitter activity, primarily ↓ **availability of serotonin and norepinephrine** and abnormalities of the limbic-hypothalamo-pituitary-adrenal axis.
- **Psychosocial causes:** loss of parents in childhood, social loss during adult life (e.g. loss of spouse), low self-esteem, loss of hope, and negative interpretation of life events (e.g. taking a genuine compliment as insincere and undeserved).

Major Depressive Disorder

Patient Example: A 45-year-old man tells his physician that he has little interest in activities he formerly enjoyed. He has lost 8 kg weight, reports that he wakes up 2 hours before his alarm goes off and cannot fall back to sleep. He says 'my family would be better off without me'. He says that, although he feels tired and 'out of sorts' most of the time, he feels somewhat better in the evening than in the morning (diurnal variation in symptoms).

Cardinal Features

- MC psychiatric disorder
- **F:M = 2:1**; mean age of onset - 40 years; symptoms should be present for **at least 2 weeks** for diagnosis.
- **Major depression** is characterized by sadness of mood and loss of interest/pleasure in almost all activities ('**melancholic**' features summarized in the following table) - resulting in social withdrawal.
- **Pessimism** - helplessness, hopelessness; worthlessness.
- Somatic symptoms: from mild hypochondriasis to **delusions of nihilism** (e.g. 'I feel like my intestines are rotting away').
- Psychotic symptoms: Can occur (depression with psychotic features) hallucinations are uncommon.
- **Pseudodementia** is seen in **depression**.

Clinical signs in depression

- **Otto Veraguth's fold:** A triangular shaped skin fold in the nasal corner of the upper eyelid;
- **Omega sign:** This is the occurrence of a fold (like the Greek letter omega, Ω) in the forehead above the root of the nose produced by the excessive action of the corrugator muscle (muscle of grief and suffering).

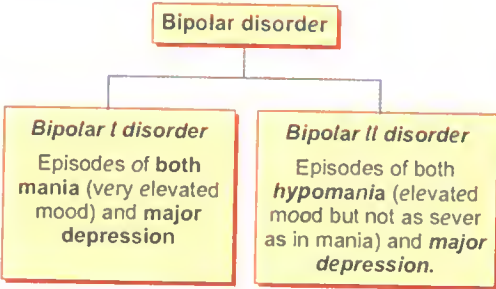
Treatment

- Selective serotonin reuptake inhibitors - **SSRIs** (*now the first line drugs*), tricyclic antidepressants and mono-amino oxidase inhibitors (MAOIs) are used. For more details of the antidepressant drugs see the section on psychopharmacology.
- **Electroconvulsive therapy** is used when *psychotic, severe, treatment refractory depressions or suicidal risk* is present.
- **Phototherapy** used for *seasonal mood disorders*.
- **Combined psychotherapy and pharmacotherapy** are the best treatment.
- **Repetitive Transcranial Magnetic Stimulation** (RTMS) is FDA approved for treating **treatment resistant depression** (also used for *migraine*).
- **Vagus nerve stimulation** has been used of *severe depression* and *intractable epilepsy*.

- In some patients with major depressive disorder, the residual phase is characterized by dysthymic disorder (**'double depression'**).
- The diagnosis of dysthymic or cyclothymic disorder is not made until the patient has had **symptoms for at least 2 years**.

Bipolar Disorders

Patient Example: A 29-year-old journalist is referred to a psychiatrist by his physician. He has become grandiose in his manner during the previous 2 months challenging the decisions of senior editorial staff and voicing his intention to take over the editorial chair. When seen he was in an elated mood, he had an inflated opinion of his abilities, was continuously talking and jumped from one subject to another. His manner was overfamiliar and he kept pacing up and down the room.



Cardinal Features

- General criteria for a manic episode require a clear period of **persistently elevated, expansive or irritable mood** (3 or 4 of the below criteria) **lasting 1 week** or severe enough to require hospitalization.
- **Criteria for a manic episode** are:
 - **Self-esteem:** *highly inflated*, grandiosity
 - **Sleep:** *decreased need for sleep*, rested after only a few hours
 - **Speech:** pressure of speech, *more talkative* than usual,
 - **Thoughts:** racing thoughts in the mind, *flight of ideas* (rapidly produced speech with abrupt shifts from topic to topic, the connections between shifts are apparent). When flight becomes severe, incoherence occurs.
 - **Attention:** easy distractibility
 - **Activity:** *increased goal-directed activity*. In hypomania there is a marked increase in productivity and creativity. Many artists and writers have contributed significantly in such periods.
 - **Hedonism:** high excess involvement in pleasurable activities (sex, spending, travel).

Melancholic ('Vegetative') Signs of Depression ('SIG-E-CAPS')

Sign	Remarks
Sleep	Insomnia and early morning awakening are common
Interest	Decrease in interest and pleasure in most activities with loss of motivation
Guilt	Patients feel excessive self-blame
Energy	Loss of vigor ('hard to get through routine tasks')
Concentration	Cognitive problems (decreased attentiveness, memory disturbances; indecisiveness)
Appetite	Decreased desire for food and sex is common (increased appetite with weight gain can also occur)
Psychomotor activity	Decreased physical activity (psychomotor retardation) is common in the elderly; less often increased physical activity (psychomotor agitation) occurs.
Suicidality	Recurrent thoughts of death, suicidal ideation, suicidal plan, suicide attempt

Dysthymic Disorder

Patient Example: A 25-year-old woman has felt 'low' since her college graduation 3 years ago. Her family members say that she never seems really happy. She resists their suggestions that she seek psychotherapy.

Cardinal Features

- Dysthymic disorder is a **chronic and less severe form** of major depression (mild/moderate) most of the time with, *no discrete episodes*.

- The depressed phase of bipolar disorder resembles depression in major depressive disorder, but the first episode may differ.
- Untreated manic episodes last approx. 3 months; there is no unipolar manic disorder since depressive symptoms eventually occur. Therefore one episode of mania or hypomania defines bipolar disorder.
- **'Rapid cycling'** = 4 or more episodes of either depression or mania in a given year; maybe a/w *hypothyroidism*.

Treatment

- **Mood stabilizers** in conjunction with benzodiazepines (for rapid tranquilization) and antipsychotics; **DOC** for treating mania is **lithium**.
- Anticonvulsants such as **carbamazepine** and **valproic acid** are also used to treat mania, particularly **rapid cycling bipolar disorder** and mixed episodes (mixed manic and depressive features).

Cyclothymic Disorder

Patient Example: A 30-year-old woman has seemed full of energy and optimism for no obvious reason (an 'up' or hypomanic period) for the last 4 months. Previously, she was described by friends and family as very sad, 'down in the dumps'.

Cardinal Features and Treatment

- Cyclothymic disorder is a **recurrent, chronic, mild form of bipolar disorder** in which mood typically oscillates between **hypomania and dysthymia** it is not diagnosed if a person has had either a manic episode or a major depressive episode.
- The diagnosis of dysthymic or cyclothymic disorder is not made until the patient has had **symptoms for at least 2 years**.

Seasonal Affective Disorder

- Patient with a mood disorder tends to experience depressive episode during a particular season **most commonly during winter for 2 continuous years** during same season.
- Treatment:
 - **Phototherapy:** Patient is exposed to light 1-2 hours before dawn or in early morning each day.
 - **Bupropion** is the DOC.

EXTRA EDGE

- MC **psychiatric sequelae** of **traumatic brain injury** is **mood disorder**.
- **Drugs** causing depression: Levodopa; beta-blockers; corticosteroids, OCPs; Reserpine, Clonidine; methyl dopa; guanethidine; Opiates; Sedatives; Alcohol.

- **Systemic illnesses** causing depression: Hypo/hyperthyroidism; cancer; stroke; chronic heart disease; AIDS; rheumatoid arthritis; multiple sclerosis.
- The maximum **DALY** (Disability Adjusted Life Years) loss is for unipolar **depression**.
- Features of melancholia occurring in the age group of 40-65 years (involutional age group) is called '**involutional Melancholia**'.

SUICIDE

- MC sex to **attempt suicide: females**
- MC sex to **complete suicide successfully: Males** (Males use better methods! - guns etc..)
- **Depression is the MC cause** of suicide in psychiatric patient; Second MC is schizophrenia.
- Among **doctors, Psychiatrists are at greatest risk** of suicide (Kaplan and Sadock, 10th edn/900).
- **Best indicator of increased risk** of suicide = **prior suicidal attempt**.
- **Low serotonin levels** are a/w depression and **suicidal behavior**.
- Incidence of suicide in population is about **10-11 per lakh** population.

POSTPARTUM MOOD DISTURBANCES

- **Postpartum (maternal) 'blues': MC type;** depressed affect, tearfulness and fatigue starting 2-3 days post delivery; **resolves in 2 weeks**.
- **Postpartum depression:** Depressed affect, anxiety; lasts **2 weeks to a year** or more; treat with antidepressants.
- **Postpartum psychosis:** Delusions/hallucinations; confusion; unusual behavior; lasts days to 4-6 weeks; antidepressants, antipsychotics and hospitalization (to prevent suicidal ideas).

Changes in DSM-5

- DSM-5 contains several new depressive disorders, including **disruptive mood dysregulation disorder** and **premenstrual dysphoric disorder**.
- Disruptive mood dysregulation disorder, is included for children up to age 18 years who exhibit persistent irritability and frequent episodes of extreme behavioral dyscontrol.
- **Removal of bereavement exclusion:** This change acknowledges the fact that bereavement and major depression are not always entirely separate. Grief following a loss (of a loved one-bereavement) is a significant psychological stressor and may trigger a major depressive episode in some individuals.

CHILD PSYCHIATRY

Pervasive Developmental Disorders

- Infantile autism
- Asperger's syndrome (MC boys)
- Rett's syndrome (affects only girls)
- Childhood disintegrative disorder
- Pervasive developmental disorder not otherwise specified

Infantile Autism

Patient Example: A 3-year-old boy shows no interest in or connection to his parents, other adults, or children. He does not speak voluntarily and is fascinated with watching rotating objects. He screams fiercely when his environment is altered in any way, such as when his mother tries to dress him (Also see Dustin Hoffman in the movie, 'Rain Man').

Cardinal Features and Treatment

- **Leo Kanner** coined the name **infantile autism**
- MC in **boys**; onset **before the age of 3 years**;
- **Defects in reciprocal social interaction:** failure to make social contact; aloofness, **poor eye contact**, etc.
- **Defects in communication:** delay/lack of language development; difficulty holding conversations; unusual/repetitive language (babbling, echolalia, perseveration, poor articulation, pronominal reversal (I-you) are common.
- Restricted **repetitive behavior** and interests: Resistance to change with associated ritualistic and/or manneristic behaviors—stereotyped behaviors like head-banging, body-spinning, hand-flicking, etc.
- **Idiot-savant syndrome:** some autistic children have **isolated well-developed skills** (rote memory, computation, musical ability).
- **Etiology:** Perinatal complications, genetic loading.
- Behavior therapy (**operant conditioning**) may reduce stereotypies.
- **Prognosis is poor** with persistent impairments in 60%.

Differential diagnosis of autistic disorder

Asperger's syndrome

- It is a mild form of autism with **later onset**;
- MC in **boys**;
- **NORMAL language** development and **intelligence**.
- **Pedantic speech** (sounds like a 'little professor') and a **preoccupation with obscure facts** often occur.

Contd...

Contd...

Differential diagnosis of autistic disorder

Rett's syndrome

- **X-linked** (MECP2 gene); affects **girls only** (affected males die in utero).
- After an apparently normal early development and normal head circumference at birth, there is **deceleration of head growth between the age of 5 and 30 months**.
- Stereotyped movements develop with **hand clapping and head wringing**. Expressive and receptive language is impaired with **mental retardation**.

Attention-Deficit Hyperactivity Disorder, ADHD (Hyperkinetic Syndrome)

Patient Example: A 7-year-old boy frequently gets into trouble at school because he interrupts the teacher, disturbs the other students, and cannot seem to sit still in class

Cardinal Features and Treatment

- Described first by **Heinrich Hoff**, a.k.a **Strauss syndrome**.
- Characterized by an **early onset (usually 3-8 years)** of **short attention span, distractibility, overactivity, impulsivity, clumsiness and language delay**, which lasts longer than **6 months**.
- MC in **boys**, present in two or more settings (**school, home, work**) and is often **a/w antisocial behavior/conduct disorder**; 50% continue to have ADHD into adulthood
- Etiology: Genetic loading, poverty, **parental alcohol abuse**, dietary constituents (**lead, tartrazine**) and **exposure to tranquilizers** (barbiturates).
- **Treatment** (CNS stimulants) is given **only when severe** and includes **the DOC - methylphenidate**; others like pemoline and dextroamphetamine are also tried.
- **Adverse effects** of CNS stimulants in children include failure to gain weight and inhibition of growth. Barbiturates are contraindicated as they **increase hyperactivity**.
- **Pemoline and imipramine** should **NOT** be given before 6 years of age.
- **Nonstimulant** drugs used for ADHD include atomoxetine, clonidine and guanfacine.

Oppositional Defiant Disorder

Patient Example: A 7-year-old boy frequently gets into trouble at school because, although he gets along well with other children, he is aggressive towards the teachers and the principal.

Cardinal Features and Treatment

- Onset is usually **before 8 years** of age.
- **Characteristics:** A pattern of **defiant, negative, noncompliant behavior toward authority figures (parents, teachers)**, although this behavior does not grossly violate social norms/NO criminality; argumentative, angry resentful and easily annoyed – **for 6 or more months**.
- May **progress to conduct disorder**, remits in one-fourth of children.

Conduct Disorder

Patient Example: A 9-year-old boy frequently gets into trouble at school because he hits the other children and has been found torturing his pet dog at home.

Cardinal Features and Treatment

- Onset before 10 years for childhood type; after 10 years for adolescent onset type.
- **Characteristics:** **behavior that violates social norms**, including aggressive behavior towards others and **towards animals, lying and stealing, destruction of property**; serious deviation from societal rules and parental rules (e.g. **truancy, running away, setting fires**).
- **A/w mood disorder, criminal behavior, antisocial personality disorder, and substance abuse** in adulthood.

Separation Anxiety Disorder

Patient Example: A 7-year-old boy refuses to sleep in his bed alone, also refuses to go to school. When questioned about his behavior, he seems anxious and says that he is afraid his mother will die.

Cardinal Features and Treatment

- MC age of onset is **7-8 years**; child has had a **stressful life event recently** (e.g. **death of a loved one**); anxiety disorders are often present in the parents.
- **Characteristics:** The child is **very reluctant to be away from his parents** because he has an overwhelming fear of loss of his major attachment figures, particularly his mother.
- Affected children refuse to go to school, '**school phobia**' and complain of physical symptoms (stomachache, headache) to avoid going to school.
- **Family therapy** is effective. The adult who has had a separation anxiety disorder as a child may be at risk for anxiety disorders, particularly **agoraphobia**.

Non-Organic Enuresis

- Enuresis is **repetitive voiding of urine at inappropriate places** (e.g. **in bed during sleep**) at least twice a month after **5 years of age**; it is **MC in boys**.
- Enuresis may be **primary** (bladder control has never been achieved) and **secondary** type (after a period of bladder control of at least one year).
- Etiology: **Psychological stress** (insecurity, sibling rivalry, death of a parent); in diurnal enuretics, an organic cause must be looked for (worm infestation, spina bifida, diabetes mellitus, seizure disorder).

Treatment for nocturnal enuresis

- The treatment of **choice is behavioral** (e.g. a buzzer and pad apparatus);
- Antidiuretic compounds such as **intranasal desmopressin acetate spray (DOC)**;
- **Oral imipramine**;
- **Reboxitine** (norepinephrine reuptake inhibitor);
- **Reassurance for the child and parents** is necessary.

MENTAL RETARDATION (MR)

- **Intelligence quotient (IQ)** = Mental age (MA) divided by chronological age (CA) multiplied by 100; i.e. **IQ = MA/CA × 100**; according to **Stanford-Binet**.
- Stanford-Binet and Weschler are the **most famous test of IQ**.

Classification of Mental Retardation

Accepted new IQ classification	Obsolete IQ classification
▪ 50-70 = Mild	▪ 70-80 = Borderline deficiency
▪ 35-49 = Moderate	▪ 50-69 = Moron
▪ 20-34 = Severe	▪ 20-49 = Imbecile
▪ < 20 = Profound	▪ < 20 = Idiot

EXTRA EDGE

- **MC cause** of mental retardation: Down's syndrome (trisomy 21).
- **MC chromosomal abnormality** causing mental retardation: Down's syndrome
- **Second MC chromosomal abnormality** causing mental retardation: Fragile X syndrome
- **MC cause of inherited mental retardation:** Fragile X syndrome.
- X-linked recessive disease with **mental retardation** and **self mutilation** is seen in: Lesch Nyhan syndrome.
- '**Contingency management reinforcement technique**' is used to modify behavior of a mentally retarded person

disappear when unnoticed); dysphonia and mutism and **globus hystericus** (i.e. lump in the throat).

- With **sensory symptoms**: 'Glove and stocking' anesthesia, paresthesia, hyperesthesia, deafness, '**tubular vision**', blindness (visual evoked potentials are normal).
- With **seizures**: Earlier known as **hysterical fits or pseudoseizures**. These can be distinguished from convulsions as follows—patient **does NOT become unconscious** although he may be unresponsive, there is **NO incontinence, cyanosis or injury** and the **tongue is NOT bitten, NO rise in postictal serum prolactin levels**. Hysterical fits **never occur during sleep**.

Dissociative Disorders

Dissociative disorders are characterized by sudden but temporary loss of memory or identity or by feelings of detachment because of emotional factors.

- Dissociative amnesia

Patient Example: A 22-year-old soldier cannot recall the events of a battle in which one-half of his platoon was killed (circumscribed amnesia).

- MC clinical type of dissociative disorder; **circumscribed amnesia** is MC.
- Dissociative fugue

Patient Example: A 34-year-old secretary who formerly lived in New Delhi has been living in Chandigarh and working as a school teacher for more than 3 years. She has no memory of coming to Chandigarh or leaving New Delhi.

- Dissociative fugue is characterized by **sudden inability to remember pertinent personal information** coupled with **wandering away from home** and taking on a new identity. The person usually is **not aware** that she has assumed a new identity.
- The onset is usually sudden in the presence of severe stress. The **termination too is abrupt** and is followed by **amnesia for the episode**, but with recovery of memories of earlier life.
- Dissociative identity disorder (multiple personality disorder)

Patient Example: A 45-year-old woman who is married and has two children usually dresses conservatively. She receives a letter containing a recent photograph of her in a short skirt and deep-necked pullover. She does not remember the person who wrote the letter. She has no recollection of purchasing the dress or posing for the photograph.

- Sudden alterations **between two or more patterns of behavior (personalities)**, each of which is forgotten by the patient when the other is present.

- Most patients are **women** and one personality usually rules the others.

- Depersonalization Disorder

Patient Example: A 45-year-old man says that he feels 'as if he is outside of himself' watching his life as though it were a movie. He knows that his perception is only a feeling and that he is really living his life.

- **Depersonalization** is characterized by recurrent and persistent feelings of **detachment from self**, mental situation and environment (**derealization** - feeling of reality of the external world is temporarily lost).
- Etiology is due to exposure to **severe psychological stress**.

More unique features

- **Ganser's Syndrome**
 - Seen more often in **prison inmates**. Central feature is '**approximate answers**' (e.g. the patient may say 2 + 2 = 5, or when asked the color of snow, reply 'green'). **Spontaneous improvement** often occurs accompanied by amnesia for the abnormal behaviors.
- '**La-belle**' Indifference
 - Patients with **conversion and dissociative disorders** (hysteria) sometimes show **inappropriate lack of concern towards their symptoms** despite the apparent severity or disability produced.
- **Abreaction**
 - Abreaction is **bringing to conscious awareness, thoughts, affects and memories for the first time**. May be achieved by hypnosis, free association or IV thiopentone. Used popularly in the **past** to treat dissociative and conversion disorders, especially those arising in battle.

Tourette's Disorder (Gille's de la Tourette)

Patient Example: A 20-year-old man with normal intelligence and social relationships has had multiple tics since he was 8 years of age. At 17, he began to clear his throat intermittently and to utter strings of curse words during conversations.

Cardinal Features and Treatment

- Tourette's patients have many **motor tics** (blinking, grimacing, shoulder shrugging, **echokineses/echopraxia**—mimicking observed acts, **copropraxia**—obscene acts).
- Most patients have at least one **vocal tic** (e.g. barking, grunting, **coprolalia**—use of obscene words - ONLY in 20%, **echolalia** - repeating other's words, **palilalia** - repeating one's own words).
- Vocal and motor tics may NOT occur concurrently.

- As per DSM 5 tics must persist for > 1 year after first tic onset.

- Onset **before age 18 years** of age; **boys** affected MC; It is **a/w OCD**.
- Etiology; alterations in **dopamine, opioids and second messenger systems**; **controversial a/w PANDAS** (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection).
- Treatment: **Alpha agonists - Clonidine and guanfacine**. For **severe tics**: **Haloperidol** is drug of choice; behavioral therapy.

Changes in DSM-V

Major changes in dissociative disorders in DSM-5 include the following:

- **Derealization** is now called **depersonalization/derealization disorder**.
- **Dissociative fugue** is now a specifier of dissociative amnesia rather than a separate diagnosis.
- The criteria for dissociative identity disorder have been changed to indicate that symptoms of disruption of identity may be reported as well as observed, and that gaps in the recall of events may occur for everyday and not just traumatic events. Also, experiences of **pathological possession** in some cultures are included in the description of identity disruption.

SOMATOFORM DISORDERS

These are characterized by physical symptoms without a sufficient organic cause. A person with somatoform disorder is not malingering and not delusional, but truly believes that he/she has a physical problem.

Somatization Disorder (Briquet's Syndrome)

Patient Example: A 50-year-old woman has a 25-year history of vague and chronic physical complaints. She says that she has always been sick, but her doctors can not identify her problem and can not help her.

- **Multiple somatic symptoms** with **NO physical disorder**; symptoms should be present for **at least 2 years** for diagnosis; involves multiple systems; presence of **conversion symptoms** is common.
- Onset before 30 years usually, MC in women; chronic and lifelong disorder, symptoms are increased by stressful life events.
- Historical **criteria** required for diagnosis:
 - 4 different pain sites or painful functions
 - 2 GI symptoms other than pain
 - 1 sexual or reproductive symptom other than pain
 - 1 pseudoneurological symptoms (impaired balance, paralysis, aphonia, urinary retention).

Hypochondriasis

Patient Example: A 45-year-old man tells the doctor that he has been 'ill' for most of his life. He has seen many doctors ('**doctor shopping**') but is angry at most of them since they referred him to psychiatrists. He now fears that he has intestinal cancer and wants the doctor to operate on him. Many of his previous 'illnesses' also seem to be exaggerated responses to normal physical sensations.

- Persistent preoccupation with a **fear or belief of having one or more serious disease(s)**, based on persons own interpretation of normal body function or a minor physical abnormality; more common in middle and old age.
- **Hypochondriasis** is believed to be based on a **narcissistic personality**.
- In DSM-5 the term hypochondriasis has been **eliminated**.

Body Dysmorphic Disorder

Patient Example: A 30-year-old woman wants rhinoplasty for her 'thick and scarred' nose and blepharoplasty for her 'sagging' eyelids. She rarely goes out in the daytime since she believes that her nose and eyes make her look like an 'old lady'. On physical examination, her nose and eyes appear completely normal.

- Excessive focus on a **minor or imagined physical defect** (usually of the face or head).
- Onset usually in late teens; level of concern varies over time.

Pain Disorder

Patient Example: A 39-year-old man had a minor injury while playing football with his son 10 months ago and now he still complains of severe knee pain although there is little or no evidence of any abnormality.

- **Persistent, distressing pain** is the main feature, **not explained** by physical causes; can be acute (6 months) or chronic (6 months) and often coexists with medical condition.
- In chronic disease, abuse and **dependence on analgesics** is common.
- **Somatoform Autonomic Dysfunction**
 - **Hyperventilation syndrome**: May be seen as a **symptom of panic attacks**.
 - **Irritable bowel syndrome**: Also called **spastic colitis, nervous diarrhea and colon neurosis**.
- **Premenstrual syndrome (premenstrual tension)**: Symptoms such as feeling of irritability, depression, crying spells and anxiety start a few days after ovulation and reach a **peak 4-5 days before menstruation** and **disappear usually around menstruation**. May be due to both hormonal alterations and psychosocial causes. Treatment consists of diuretic to counter water retention and restricting fluid and electrolyte intake.

Munchausen syndrome

- Synonyms — *hospital addiction, factitious disorder or hospital hobo*.
- This term is used for those patients who repeatedly simulate or fake diseases for the sole purpose of obtaining medical attention. There is NO other recognizable motive, hence different from malingering.
- Patient gains many hospital admissions through deception, feigning illness, (*pseudologia fantastica*) hoping for a laparotomy (*laparotomophilia migrans*) or bleeding alarmingly (*hemorrhagic histrionica*) or presenting with curious fits (*neurologica diabolica*) or false heart attacks (*cardiopathia fantastica*).
- Abdomen may show multiple scars of previous surgeries ('grid-iron' abdomen).
- Munchausen syndrome **by Proxy**: The parents seek repeated medical assistance for their children giving false accounts of symptoms and faking signs.

Changes in DSM-V

Somatic Symptom and Related Disorders

- In DSM-5, **somatoform disorders** are now referred to as **somatic symptom disorders**.
- Diagnoses of *somatization disorder*, *hypochondriasis*, *pain disorder*, and *undifferentiated somatoform disorder* have been **removed**.
- Somatic symptom disorders include
 - Illness anxiety disorder
 - Conversion disorder (functional neurological symptom disorder)
 - Psychological factors affecting other medical conditions
 - Factitious disorder.

FEATURES OF PERSONALITY DISORDERS

CLUSTER 'A' (Odd/Eccentric = 'Weird')

- Paranoid** *Suspicious of fidelity of spouse, hypersensitive, distrustful; projection is the major defense mechanism*
- Schizoid** *Emotionally cold, voluntary social withdrawal without psychosis, limited emotional expression.*
- Schizotypal** *Inappropriate/constricted affect, ideas (not delusions) of reference, magical thinking, unusual perceptions (e.g. bodily illusions), odd ideas (about telepathy), superstitious.*

CLUSTER 'B' (Flamboyant, dramatic = 'Wild')

- Antisocial (psychopathic, sociopathic)** *Collous disregard for the rights or safety of others, failure to maintain enduring relationships, low frustration tolerance and aggressive threshold, incapacity to experience guilt or profit from adverse experiences (e.g. punishment), a/w drug abuse*

Contd...

Contd...

CLUSTER 'B' (Flamboyant, dramatic = 'Wild')

- Borderline (impulsive)** *Unstable relationships, impulsive behavior (reckless spending, binge eating or sex), self-mutilation; boredom and sense of emptiness; splitting is a major defense mechanism*
- Histrionic** *Self-dramatization, excessive shallow (dramatic) emotionality, attention seeking, suggestibility (easily influenced by others), inappropriate sexually provocative*
- Narcissistic** *Grandiosity; lacks empathy, requires admiration; demands the 'best' and reacts to criticism with rage*

CLUSTER 'C' (Fearful/anxious = 'Worrying and Wimpy')

- Avoidant (Anxious)** *Persistent feelings of tension and inadequacy, social inhibition, introvert, restriction in lifestyle to maintain physical security. This disorder is an epitome of what is called inferiority complex.*
- Dependent (Asthenic)** *Allowing others to make most of one's important life decisions, submissive and clinging; needs to be taken care of*
- Obsessive-Compulsive (Anankastic)** *Rigidity of thinking; perfectionism; preoccupation with rules, order, and schedules. Major depressive episodes are frequent. These are ego-syntonic life traits with no obvious onset. (Note: Obsessive compulsive disorder is egodystonic)*

EXTRA EDGE

Dialectical behavior therapy (DBT) is a **cognitive-behavioral approach** that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. *Useful in the treatment of personality disorders (especially in borderline and those with intentions of chronic suicidality).*

SLEEP DISORDERS

Dyssomnias

- Dyssomnias are characterized by problems in the timing, quality or amount of sleep.
- They include **insomnia, hypersomnia, narcolepsy, sleep apnea and circadian rhythm sleep disorder**.

Parasomnias

- Parasomnias are characterized by abnormalities in physiology or in behavior associated with sleep.
- They include the below mentioned **non-REM sleep disorders and nightmare disorders**.

Changes During the First 3 Hours of Sleep

- Increased:** HGH (Human Growth Hormone); Prolactin; Serotonin.
- Decreased:** Dopamine, TSH

Stages of Sleep and the EEG

Sleep stage and EEG waves	Features
Awake	
• Beta	Active mental concentration
• Alpha	Relaxed with eyes closed
Non REM sleep (75% sleep time)	
Stage 1	5% of sleep time
• Theta (4-6 Hz); low voltage alpha; vertex sharp waves	Lightest stage of sleep characterized by peacefulness, slowed pulse and respiration, decreased BP and episodic body movements
Stage 2	Largest percentage of sleep time (45%)
• Sleep spindles (12-14 Hz) and high amplitude 'K' complexes	
Stages 3, 4; Slow Wave Sleep (SWS); Delta sleep	25% of sleep time (decreases with age)
• High amplitude low frequency, 2 Hz, delta waves	Deepest, most relaxed stages of sleep a/w sleep disorders mentioned below: SWS is most prominent in childhood (growth hormone secretion occurs) and in the healthy elderly male, SWS maybe completely absent
• Stage 3 = < 50 % delta waves with sleep spindles	
• Stage 4 = > 50% delta waves but NO sleep spindles	
Rapid Eye Movement (REM) sleep (25% sleep time)	
• 'Sawtooth' beta, alpha and theta waves	Also called — dream sleep, D state sleep, paradoxical sleep (REM occur, BUT sleep is deep!). Eye movements are recorded by EOG (electrooculogram).
• Low amplitude, Low voltage high frequency waves are seen on EEG like in awake state.	25% of sleep time (decreases with age)
• EMG activity is absent.	Dreaming: penile and clitoral erection; increased pulse, respiration, BP and gastric motility; low skeletal muscle tone and paralysis

Stages 3 and 4 (Slow Wave) Sleep Disorders

- Night terrors (Pavor nocturnus)** = MC in boys; runs in families; can be a precursor to **temporal lobe epilepsy**; the repetitive experience of **fright in which a person (usually a child) screams in fear**. The child cannot be awakened and **cannot remember the dream**.
- Sleep walking (Somnambulism)** = Begins in childhood (4-8 years); the person walks around without being conscious and **DOES NOT REMEMBER** the episode.
- Sleep talking = Somniloquy**
- Nocturnal enuresis = Bed wetting**
- Bruxism = Teeth grinding**; typically occurs at night, a/w daytime anxiety, can lead to dental malocclusion.

REM (Desynchronized or Paradoxical) Sleep Disorders

- Nightmare disorder**: Repetitive frightening dreams that cause nighttime awakenings and the person can **usually recall** the nightmare; common in **ages 3-7**; desensitization behavior therapy.
- Narcolepsy**
- Insomnia**
- Sleep apnea**

Narcolepsy (Gelineau's Syndrome)

Patient Example: A 21-year-old medico, who goes to sleep at 11 PM and wakes at 7 AM, falls asleep in the lab every day. He had a few minor car accidents that occurred because he fell asleep while driving.

- Common in the 15-25 year age group; a/w **HLA DR2** and is a REM sleep disorder
- It is a/w **deficiency of hypocretin** (a.k.a **orexin**) due to **anti trlb 2 antibodies**.
- It is characterized by
 - Sleep attacks** – MC, due to short REM latency
 - Cataplexy** – sudden physical collapse because of loss of all muscle tone after a strong emotional stimulus.
 - Hypnagogic** (occur while GOing to asleep) or **hypnopompic** (just as the patient wakes up) hallucinations
 - Sleep paralysis** – in which the body is paralyzed for a few seconds after waking.
- Modafinil** is the DOC. **Methylphenidate** is a common II choice.

Insomnia

Patient Example: A 30-year-old man says that most nights during the last year he has lain awake in bed for more than 2 hours before he falls asleep. His sleep is often interrupted. The next day he is tired and forgetful and often makes mistakes in his work.

Cardinal Features

- Insomnia is a **difficulty in falling asleep or staying asleep** that occurs at least **three times per week** for at least **one month** and leads to sleepiness during the day or interferes with social or occupational functioning.
- Etiology:** Medical conditions (pain, endocrine and metabolic disease); substance abuse (caffeine) and withdrawal; anxiety and depressive disorders.
- Treatment:** *avoid coffee before bedtime, daily exercise (but not just before sleep); relaxation techniques; limited use of BZDs to establish an effective sleep pattern (e.g. flurazepam 15-30 mg or zolpidem 10 mg at bedtime for 1-2 weeks); Ramelteon (melatonin MT1 and MT2 receptor agonist).*

Sleep Apnea

Patient Example: An overweight 50-year-old man reports that he is sleepy all day despite having 8 hours of sleep at night. His wife reports that his loud snoring keeps her awake.

Cardinal Features

- Patients with sleep apnea *stop breathing briefly* (cessation of breathing for about 10 seconds; at least 30 episodes); low oxygen or high carbon dioxide level in the blood **awakens the patient repeatedly during the night**, resulting in *daytime sleepiness*.
- In patients with *central sleep apnea* (more common in the elderly), no respiratory effort occurs.
- In patients with **obstructive sleep apnea (OSA)**, which is MC in *men* (M:F=8:1), in people 40-60 years old, and in the **obese (Pickwickian syndrome)**, respiratory effort occurs, but an airway obstruction prevents air from reaching the lungs. Patients often *snore*.
- Sleep apnea is related to **depression, headaches, and pulmonary hypertension**, and also may result in *sudden death during sleep* in the elderly and in infants.
- **Epworth sleepiness scale** screens for OSA; measures general level of *daytime sleepiness*.
- Treatment consists of **weight loss and avoidance of alcohol (if appropriate, first choice); nasal continuous positive airway pressure (CPAP, 11 best choice)**, and **uvulopalatopharyngoplasty** (rarely).

EATING DISORDERS

Etiology

- MC in *women* (>90%); more common in *late adolescence and young adulthood*, in high academic achievers and **high socioeconomic groups**; more prevalent in

Physical Characteristics

	Anorexia nervosa	Bulimia
• Method of weight control	Restriction of Intake	Vomiting
• Binge eating	Uncommon	Common
• Weight at diagnosis	Markedly decreased	Near normal
• Ritualized exercise	Usual	Rare
• Amenorrhea	100%	50%
• Other endocrine changes	Common (LOW estrogen, testosterone, LH, FSH; hypoglycemia)	Uncommon
• Antisocial behavior	Rare	Frequent
• Cardiovascular changes (Bradycardia, hypotension)	Common	Uncommon
• Skin changes (lanugo hair, carotenemia, dryness)	Usual	Rare

developed countries where there is plenty of food, **anorexia** is often associated with a stressful life event (like going to college).

Anorexia Nervosa

Patient Example: A 20-year-old model says that she needs to lose 13 kg to pursue a career in modeling. She is 5 feet 8 inches tall and weighs 53 kg. Her mood is good. Findings on physical examination are normal except for excessive growth of body hair. She reports that she has not menstruated in more than a year.

- Characteristics: **Excessive dieting; refusal to eat** despite **normal appetite** ('anorexia' is a misnomer); **abnormal behavior dealing with food** (e.g. cutting food into very small pieces; simulating eating; collecting recipes and cooking for others) **weight loss** leading to body weight 15% below expected; the absence of at least three consecutive menstrual cycles.
- Treatment: Structured behavioral therapy, intensive psychotherapy, and family therapy may be tried.

Bulimia Nervosa

Patient Example: A 21-year-old medical student has a parotid gland abscess. She is of normal weight for her height, but is distressed when you question her about her eating habits. She has eroded skin over the knuckles (from putting fingers into the mouth to induce vomiting).

- Psychological characteristics: **Binge eating** (in secret) of high-calorie foods usually **followed by vomiting or other purging behavior** to avoid weight gain; **poor self-image**; serious concern about gaining weight; **illness over the binge eating**.
- Treatment: Cognitive and behavioral therapies (CBT); Antidepressants (SSRIs); group therapy and family therapy.

Contd...

Contd...

	Anorexia nervosa	Bulimia
• Hypothermia	Usual	Rare
• Medical complications	Hypokalemia, cardiac arrhythmias	Hypokalemia, cardiac arrhythmias; dental enamel erosion, callus on dorsum of hands (Russell's sign); aspiration of gastric contents, esophageal or gastric rupture, parotitis
• Prognosis	Variable	Better than anorexia nervosa

Other Eating Disorders

- **Pica**: is diagnosed when the **individual, over age 2**, eats one or more **nonnutritive, nonfood substances** for **a month or more** and requires medical attention as a result. There is usually **no specific aversion to food in general** but a **preferential choice** to ingest substances such as **clay, starch, soap, paper, or ash**.
- **Rumination disorder**: individuals who have **no demonstrable associated gastrointestinal or other medical condition** repeatedly **regurgitate their food after eating** and then either **re-chew or swallow it or spit it out**. The behavior typically occurs on a **daily basis** and must persist for **at least 1 month**.
- **Avolant/restrictive food intake disorder**: Avoidance or restriction of food intake, usually stemming from a **lack of interest in or distaste of food** and a/w **weight loss, nutritional deficiency**, dependency on nutritional supplementation, or marked impairment in psychosocial functioning, either alone or in combination.
- **Binge-eating disorder**: is distinguished from bulimia nervosa by the absence of compensatory behaviors to prevent weight gain after an episode and by a lack of effort to restrict weight gain between episodes.

Changes in DSM-V

- The core diagnostic criteria for **anorexia nervosa** are conceptually unchanged from DSM-IV with one exception: the requirement for **amenorrhea** has been eliminated.
- The only change to the DSM-IV criteria for **bulimia nervosa** is a reduction in the required minimum average frequency of binge eating and inappropriate compensatory behavior frequency **from twice to once weekly**.

IMPULSE CONTROL DISORDERS

- Patients with impulse control disorders are unable to resist engaging in behavior that is harmful to themselves or other people.

- Patients usually **experience increased tension before the behavior and relief or pleasure after the behavior is completed**.
- **Treatment is by SSRIs** and sometimes, antipsychotics (e.g. in trichotillomania) or anticonvulsants (e.g. carbamazepine in intermittent explosive disorder).

Kleptomania

- Patient Example:** A 35-year-old computer engineer is caught taking an inexpensive pen from a store without paying for it. He has been caught shoplifting twice before.
- Kleptomania is the **impulse to take ('steal') things** without paying for them (even if they are affordable and not needed). **Taking the object**, rather than owning, the object is the intent. The theft is **not** an act of defiance or anger.
 - It is present in 25% of patients with **bulimia nervosa**. May be related to family dysfunction in childhood. It is a **chronic condition**; arrest, legal punishment and shame are common.

Pyromania

- Patient Example:** A 30-year-old man with an IQ (intelligence quotient) of 70 is arrested after he is found setting fires in his office building.
- Pyromania is characterized by **repetitive fire setting** and overwhelming interest in and attraction to fires; patients may become **volunteer firefighters** to be close to fires!
 - More common in **men** and mentally retarded people; often seen in conduct disorder in childhood.

Trichotillomania

- Patient Example:** A 30-year-old woman wears a wig because she has pulled out all the hair from the back of her head.
- Patients with trichotillomania have an **irresistible urge to pull out their hair** and the result is irregular patchy hair loss unilaterally on side of the dominant hand.

Pathological gambling

- Patient Example:** A 45-year-old man is afraid to tell his family that he has lost more than ₹ 20 lakhs in gambling. He has run up into debt twice this way before.
- Patients have an **overwhelming need to gamble** that negatively affects family and work relationships.
 - Gamblers anonymous (12-point program modelled after Alcoholics Anonymous) is most effective.

Contd...

Contd...

Intermittent explosive disorder (IED)
Patient Example: A 35-year-old man is arrested for leaving his car and physically attacking another motorist at a traffic light. A witness reports that the victim had overtaken the man at the previous traffic light.
• IED is characterized by episodes in which the patient loses self-control and attacks another person without adequate cause . Formerly called 'episodic dyscontrol syndrome'.
Impulse control disorder Not Otherwise specified
Oniomania (compulsive shopping); Internet addiction; Sexual addiction
Oniomania
• Compulsive shopping or buying

SUBSTANCE ABUSE DISORDERS

Alcoholism

- According to **Jellinek's classification**, **gamma alcoholism** is malignant alcoholism and **epsilon alcoholism** is **dipsomania** (compulsive-drinking).
- MAJOR site of **alcohol absorption** is from the **proximal small intestine**.
- **Metabolism** of alcohol: MAJOR pathway = In cell cytosol, **alcohol dehydrogenase** acts on ethanol producing **acetaldehyde** which is destroyed by **aldehyde dehydrogenase** in cytosol and mitochondria.
- 40% of **Japanese** have **aldehyde dehydrogenase deficiency** and are more susceptible to effects of alcohol.
- **CAGE, MAST** (Michigan Alcohol Screening Test) and **AUDIT** (Alcohol Use Disorders Identification Test) questionnaire helps in identifying **alcohol addiction**.
- Alcohol **acutely increases dopamine levels** in the brain (ventral tegmentum) leading to continued alcohol craving.

Organs Affected by Alcohol

Liver	(Normal in 50% of alcoholics); Fatty liver —acute and reversible, but may progress to cirrhosis if drinking continues; hepatitis (fever, jaundice and vomiting)— 80% progress to cirrhosis . Biopsy shows Mallory bodies ± neutrophil infiltrate. ↑ GGT (Gamma glutamyl transferase > 35U), ↑ SGOT/SGPT
Gut	Obesity; diarrhea; gastric erosions; peptic ulcers; varices; pancreatitis (acute and chronic)

Contd...

Contd...

CNS	Poor memory, retrobulbar optic neuropathy (centrocecal scotoma); cerebellar (vermis) degeneration; brain atrophy (widened sulci and ventricles); fits; falls; Wernicke's encephalopathy (ophthalmoplegia - VI nerve MC, ataxia, confusional state) ± Korsakoff's syndrome (retro and anterograde amnesia, impaired memory for new events, confabulation, mammillary bodies atrophy). Thiamine and B complex may help; Bergmann gliosis (Purkinje cell loss) in brain; decreased alpha activity on EEG
Blood	MCV ↑; anemia from—marrow depression, hemolysis, alcoholism-associated folate deficiency, GI bleeds, sideroblastic anemia, CDT (carbohydrate deficient transferin)
Heart	Arrhythmias, BP ↑, cardiomyopathy, holiday heart (arrhythmias after binge drinking, MC, atrial fibrillation)
Cancer	Breast, oral, esophageal, rectal, liver
Psychiatric	Personality deterioration; depression, suicidal behavior; erectile dysfunction and delayed ejaculation; morbid (pathological) jealousy ; fixed delusions

Alcohol Withdrawal

- Occurs **within 1-2 days of abstinence** and is characterized by **acute tremulousness** (tremor and MC feature) affecting the hands, legs and arms ('the shakys'); nausea; sweating; lability of mood (**he goes one minute and becomes sad next minute!**); incoherence and transient hallucinations or illusions (mostly visual). Later there may be epileptic **seizures**.
- Finally **after about 48 hours, delirium tremens** may develop - characterized by clouding of consciousness with disorientation in time and place, **visual hallucination** (of snakes and bugs); **tactile hallucination** of insects crawling over the body (**formication**); **Lilliputian hallucinations** (objects appears small)
- **Alcoholic hallucinosis**. This syndrome occurs during heavy drinking or on withdrawal and is characterized by **auditory hallucinations**.

Blood Alcohol Levels and its Effects

Blood Level, g/dL	Usual Effect
0.02	Decreased inhibitions, a slight feeling of intoxication
0.08	Decrease in complex cognitive functions and motor performance

Contd...

Blood Level, g/dL	Usual Effect
0.20	Obvious slurred speech, motor incoordination, irritability, and poor judgment
0.30	Light coma and depressed vital signs
0.40	Death

Acute Alcohol Intoxication

- **Stage of excitement** - well-being and euphoric feeling
- **Stage of incoordination** - slurred speech, staggering gait, pupils are dilated, **blackouts** (temporary anterograde amnesia)
- **Stage of narcosis** - deep sleep; rapid pulse; pupils are constricted but on pinching the face/neck they dilate and slowly return to their original size (**McEwan's sign**).

Terminology According to Blood Alcohol Levels

- 10 mg% = Sober
 - 20-70 mg% = Drinking
 - 80-100 mg% = Under the influence
 - 150-300 mg% = Drunk or intoxicated
 - 400 mg% and above = Coma and death
- As per section 185 of Indian Motor Vehicle Act, 1988 breath alcohol test is admissible. The statutory limit of alcohol is 30 mg%.

Testing for Alcohol

- **Blood alcohol** concentration is the **most useful** measure.
- **Widmark's formula** is used to estimate blood alcohol level.
$$a = prc \text{ (Widmark's formula), where}$$
 - a = total amount of alcohol (in grams) absorbed in the body
 - p = weight of the person (in Kg)
 - r = constant (0.68 in man and 0.50 in women)
 - c = concentration of alcohol in blood (in g/kg)
- For estimating **alcohol in urine**, the formula is
$$a = 3/4 prq, \text{ where}$$
 - q = concentration of alcohol in urine (in gram/liter) and a, p, r are the same as above.

Breath Alcohol Testing

- There are 4 types of instruments, each with its own methodology.
 - 1. **Gas chromatography-mass spectrometry** is **most specific**. Not used routinely in the field since it is expensive and not easily portable.

2. Chemical oxidation and photometry (**breathalyzer/drunkometer**): It uses the principle that alcohol is easily oxidized to acetic acid by oxidizing agents such as **potassium dichromate**.
 3. **Infrared** method (Intoxilyzer, datamaster, BAC verifier).
 4. Electrochemical fuel cell devices.
- All breath alcohol tests rely on calculating blood alcohol concentration from breath alcohol concentration - this is based on **Henry's law**.
 - Other tests are—**Alcohol dehydrogenase** method, **Kozelka and Hine** test; **Cavett** test.

Treatment

- **Alcohol withdrawal symptoms: Detoxification** - **DOC benzodiazepines** (Chlordiazepoxide and diazepam); **Clonidine** suppresses cardiovascular signs of withdrawal and has some anxiolytic effect and maybe used.
- The best way to stop alcohol is to **stop it suddenly**.
- Supplement with **thiamine** and vitamin B complex.
- Treatment of Wernicke's: IV Thiamine in 5% glucose solution. Ophthalmoparesis recovers earliest.

Anti-Craving Agents/Deterrent Agents

These are drugs used to treat alcohol dependence by encouraging abstinence from alcohol.

FDA approved drugs

- **Disulfiram** (antabuse): It is an **aldehyde dehydrogenase inhibitor** that causes **acetaldehyde** to accumulate in the blood resulting in intense nausea, headache and flushing when the patient subsequently drinks alcohol—thus acts by causing unpleasant reaction if alcohol is consumed.
- **Naltrexone**: **Pure opioid antagonist**; available as oral tablet and IM injection (once monthly)—acts by decreasing the pleasurable effects of alcohol.
- **Acamprosate**: Reduces the unpleasant feelings brought on by alcohol abstinence.

Other drugs

- **Drugs under investigation** for alcohol dependence:
 - **Varenicline** (nicotinic receptor agonist)
 - **Topiramate** (anticonvulsant)
 - **Ondansetron** (serotonin antagonist)
 - **Prazosin** (alpha-adrenergic agonist)
 - **Baclofen** (GABA-B receptor agonist)
 - **Cannabinol** receptor antagonists
- **Also Know:** Drugs causing disulfiram like reaction include: **Citrated calcium carbide**, **Metronidazole**, **Nitrafazole**, **Methyltetrazolethiol**, **Animal charcoal**, a fungus (**coprinus atromentarius**), **sulfonylureas** and certain **cephalosporins**.

- **Rehabilitation:** **Alcoholics Anonymous**.
- **AVOID phenytoin** in chronic alcoholics since phenytoin levels are lowered and there is a lower threshold for seizures.

OTHER SUBSTANCE ABUSE DISORDERS

Opioids

- Opium is the dried juice obtained by incision of the **unripe capsule of the white poppy**, *Papaver somniferum*.
- Natural derivatives of opium - **morphine**, **heroin (brown sugar or smack)** and **codeine**.
 - MC abused opioid is **Heroin (diacetylmorphine)**-in fact it is the **2nd MC** abused substance after alcohol.
 - Used IV or smoked: it causes **euphoria and tranquility/sleepiness (the 'rush' and the 'nod')**.
- **White forth from mouth** may be seen during **autopsy**.
- **Adulterants of heroin** ('cutting agents') are chalk, fructose, sucrose, powdered milk, caffeine, paracetamol, noscapine and scopolamine.

Acute opioid intoxication

- Euphoria, Hallucination, **respiratory depression**, **Hypothermia**, **Hypotension**, **cyanosis**, **pinpoint pupil**.
- Treatment of acute intoxication: **IV naloxone** is the DOC followed by **oral naltrexone**.

Opioid Withdrawal Syndrome

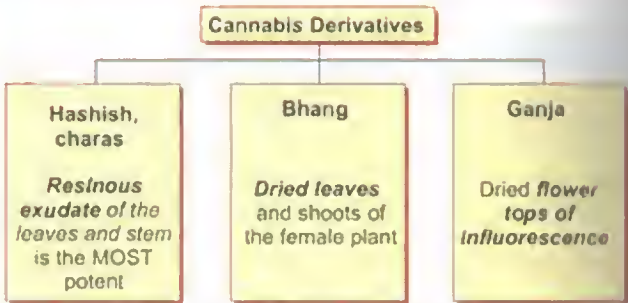
- Grade 0 = craving and anxiety
- Grade 1 = **yawning, lacrimation, rhinorrhea, and sweating**
- Grade 2 = previous symptoms plus **mydriasis, piloerection - gooseflesh ('cold turkey')**, anorexia, tremors ('**kicking the habit**'), and hot and cold flashes with generalized aching
- Grades 3 and 4 = increased intensity of previous symptoms and signs + increased temperature, BP, pulse, and respiratory rate.
- In withdrawal from the most severe addiction, **spontaneous ejaculation or orgasm** commonly occur.

Treatment:

- Detoxification: **methadone (MC)** or **buprenorphine**; for rapid detoxification: **clonidine + naltrexone**.
- Maintenance: **methadone (MC)** or **buprenorphine**; **subcutaneous naltrexone implants** can be used **ONLY** after detoxification to **prevent relapses** (contraindicated in liver disease).

Cannabis/Marijuana

Cannabis is derived from the **hemp plant**, *Cannabis sativa*; most active principle is **tetrahydrocannabinol**.



Features of Cannabis Intoxication

- **Smoking** is MC method of use
- **Conjunctival reddening**; mild tachycardia, dry mouth, increased appetite ('the munchie'); **synesthesia** (reflex hallucination—stimulation of one sensory modality produces sensation of other modality - ex, when light flashes patient gets tingling sensation!!)
- **'A motivational syndrome'**
- **Flashback phenomenon** - experiences features of cannabis use without actually using it.
- **Run amok** - psychotic episode where person goes on the rampage destroying things and killing others.
- Hemp insanity.

Therapeutic use of cannabis/marijuana

- It is used as oral cannabinoid - **dronabinol**.
 - **Antiemetic** effects in chemotherapy recipients,
 - **Appetite-promoting** effects in AIDS patients,
 - **Reduction of IOP** in glaucoma, and
 - **Reduction of spasticity** in multiple sclerosis.

Amphetamines

- Acute amphetamine intoxication may present as **paranoid schizophrenia—amphetamine psychosis** (delusion of persecution and auditory/visual hallucinations) **in clear consciousness**; hypertension, angina, sudden death; **tactile hallucinations** are seen on chronic use.
- **Liquid gold** is a slang used for **urine of amphetamine addicts** - since 40% amphetamine is excreted in urine.
- **Acidification of urine** facilitates the elimination of amphetamines.

Cocaine

- Cocaine is a **stimulant, local anesthetic, potent vasoconstrictor** derived from coca plant (*Erythroxylon coca*).
- Cocaine **hydrochloride** is the MC used form; **free base**, a purer (and stronger) derivative is called '**crack**'.

- Methods of use: **chewing** coca leaf; **snorting** - MC and least dangerous method (inhaling thru straw - can cause **nasal septal perforation**); **IV**; **smoking**.
- **Cocaine + alcohol = cocaethylene** by liver - gives more pleasure.
- **Cocaine + heroin** by injection = **speedball**.

Chronic Cocaine Abuse

CVS collapse; CNS symptoms (Seizures, strokes, migraine); obstetric (spontaneous abortion, abruptio placentae, teratogenic effects, delayed fetal growth, and prematurity); **cocaine psychosis-persecutory delusions with Magnan's sign** (**tactile hallucination of bugs** crawling under the skin, **formication**); **black** pigmentation of tongue and teeth occur.

- Acute **cocaine overdose**: **hyperadrenergic** state characterized by **hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias**; treat with **IV diazepam**.
- Dopamine agonist bromocriptine reduces cocaine craving.

LSD

- Lysergic acid diethylamide - a potent **hallucinogen**.
- Acute symptoms: **Tachycardia, hypertension, pupillary dilation, tremor, and hyperpyrexia** occur within minutes of oral intake.
- Bizarre mood changes, including **visual illusions, synesthesia** (**sounds can be seen and colors can be heard!**), and extreme lability of mood, usually occur within 30 min after LSD intake.
- The MC acute medical emergency a/w LSD use is a panic episode (the '**bad trip**'), which may persist up to 24 h; this is managed by supportive reassurance ('**talking down**').
- **Abrupt abstinence** following continued use **does not** produce withdrawal signs or symptoms. **NO specific treatment** required.

Drugs of Abuse—Slang

Drug of Abuse	Other Names
Amphetamines	Speed; Whiz; Billy; Pink champagne
Amyl nitrate	Goldrush; poppers; snappers
Barbiturates	Barbs; Idiot pills
Cocaine	Coke; Charlie; Rock, crack; nuggets; wash; gravel; snow; white lady
Dihydrocodeine	Dfs
Drug-induced sleep	Gauching; nodding; going on the nod

Contd...

Contd...

Drug of Abuse	Other Names
Drug intoxication	Stoned; wiped out; bladdered
Heroin	Smack; nasty; gear; brown; Harry scag
Ecstasy (MDMA)	XTC; echo; disco biscuit; lovedrug; (Methylenedioxy-methamphetamine)
Febrile reaction	Bad hit
Injecting SC	Skin popping
Injecting IM	Muscle popping
Injecting Subclavian	Pocket shot
Injecting through main veins	Mainlining
LSD	Acid trips; cardboard; tabs; purple haze
Marijuana	Weed; pot; draw; ganja; grass; resin; Mary; Hash
Methadone	Mud
Mickey Finn	Chloral hydrate with alcohol
Opiate withdrawal	Turkeying; clucking
Phencyclidine (PCP)	Angel dust ; KJ; ozone; missile, peace pill, hog
Physeptone ampoules	Amps
Smoking cocaine	Bonging
Smoking heroin	Chasing the dragon
Temazepam	Temazies; eggs; jellies
White heroin	China white
Zopiclone	Zim Zims
Abrus precatorius	ghonchi
Capsicum	Hunan hand

EXTRA EDGE

- **Caffeine** is the **most widely used mood altering drug** in the world.
- MC substance abuse in **India** is alcohol > **tobacco**.

SEXUAL DYSFUNCTIONS

- **Hypoactive sexual desire**
 - **Frigidity**; Decreased interest in sexual activity in **women**.
- **Excessive sexual drive**
 - Rarely, both men (**satyriasis, Don Juanism**) and women (**nymphomania**) may complain of excessive sexual drive as a problem.
- **Male erectile disorder/Impotence**
 - MC organic cause is diabetes mellitus.
 - **Normal nocturnal penile tumescence** differentiates psychogenic from organic erectile dysfunction.

Contd...

Contd.

- **Orgasmic disorder**
 - Inability to achieve orgasms despite adequate genital stimulation.
- **Premature ejaculation**
 - Ejaculation before the man would like it to occur (ejaculation before the completion of satisfactory sexual activity for both partners).
- **Non-organic vaginismus**
 - Involuntary painful spasm of the outer one-third of the vagina, interfering with coitus.
- **Non-organic dyspareunia**
 - Persistent pain a/w sexual intercourse; can occur in men.

Treatment

- Sex therapy
- Behavior therapy and relaxation techniques, including hypnosis and specific behavioral techniques such as **Master and Johnson's technique (dual sex therapy)**—**Seman's squeeze** technique (for premature ejaculation) and **sensate focus** exercises; Hegar's dilators and relaxation for vaginismus
- **Sildenafil (viagra), tadalafil, and vardenafil are phosphodiesterase 5 inhibitors** used orally for the treatment of penile erectile dysfunction usually 1 hour prior to intercourse.

EXTRA EDGE

Sexual paraphilias have been discussed in forensic medicine chapter (Pg 521).

MORE HIGH YIELD POINTS

- **Alice in Wonderland syn:** Disturbance of one's view of oneself (intrapsychic time passes too fast) seen in epilepsy, migraine, or on falling asleep.
- **Couvade syn:** Experience of symptoms resembling those of pregnancy (abdominal swelling, spasms, nausea and vomiting, etc.) in expectant fathers.
- **Ekbom's syn:** Delusional parasitosis (**Dermatozoenevahn**), although, the term is also used to describe a neurological syndrome of 'restless legs'. Some patients, middle-aged to elderly women present to dermatologists about insects or other objects in the skin.

Kleine-Levine/Klüver-Bucy syndrome

- Due to lesions of **anterior temporal horns or amygdala**; affects mainly in young males, a/w antecedent neurologic insults (trauma, HSV encephalitis); remits after age 40.
- Characterized by hypersomnic attacks (3–4 times a year lasting up to 2 days), hyperphagia, hypersexuality, hyperorality, hyperdocility (placidity), rage and confusion on awakening, visual agnosia (inability to recognize familiar faces, objects or their use); hypermetamorphopsia (tendency to shift attention frequently).

- **lactatio capitis nocturna:** Nocturnal headbanging
- **Déjà vu:** Recognition of events that are in fact new as though they have been encountered before; may be normal or a/w temporal lobe epilepsy.
- **Jamais vu:** Failing to recognize events that have been encountered before.
- **Déjà pensé:** A completely new thought sounds familiar to the person and he feels as he has thought the same thing before at some time.
- **Déjà entendu:** Illusion that one is hearing what one has heard previously.
- **Autokabalesis:** Term for committing suicide by jumping from high place.
- **Bouffée délirante** is a French term used in the past for acute and transient psychotic disorders.

Kübler-Ross Model

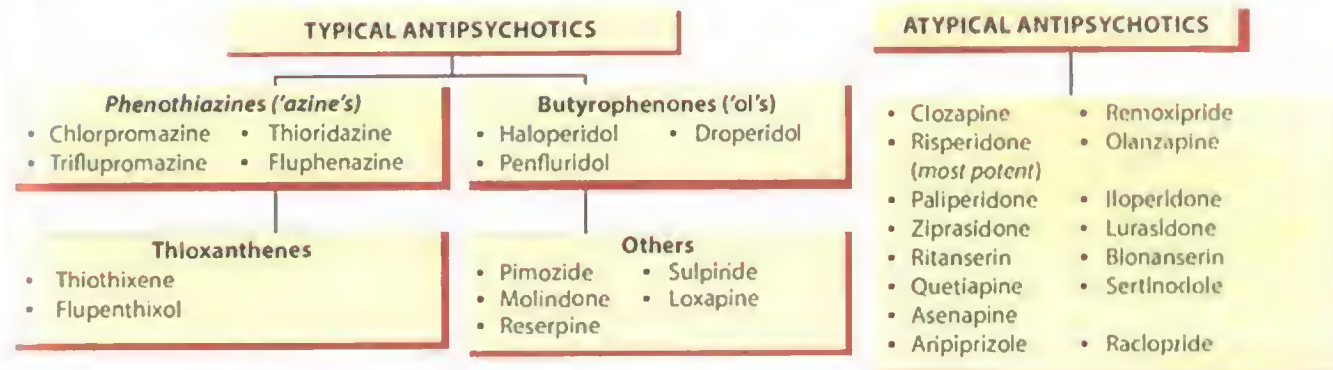
Ross described the **5 stages of adjustment to grief**, a series of emotional stages experienced when faced with impending death or death of someone. The 5 stages are (DABDA):

- **Denial** ('This is not happening to me.')
- **Anger** ('How dare God do this to me.')
- **Bargaining** ('Just let me live to see my son graduate.')
- **Depression** ('I can't bear to face going through this, putting my family through this.')
- **Acceptance** ('I'm ready to die, I don't want to struggle anymore.')

- **Personality changes** are seen in lesions of **frontal lobe**
- **Alexithymia** and is defined as the **inability to recognize emotions** and their subtleties and textures.
- **Mutism and akinesia** in a person who appears awake and even alert, is described a **stupor**.
- **Marchiafava-Bignami syndrome:** Wine/alcohol induces **degeneration of the corpus callosum**, leading to seizures, tremors, ataxia, excitement and apathy.
- **Marchiafava-Michell syndrome:** Paroxysmal nocturnal hemoglobinuria.
- **Claparede's paradox** refers to **retention of non-verbal and implicit memory** in sufferers of **Korsakoff's syndrome**.
- **Würgstimm:** refers to **speaking in an odd muffled or strangled voice**; mainly seen in **schizophrenia**.
- **Persuasion** was seen as an essential skill of living—'the art of winning friends and influencing people' as the famous **Dale Carnegie** put it.
- **Consultation Liaison psychiatry** is the subspecialty of psychiatry concerned with medically and surgically ill patients.

ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

Classification



Mechanism of Action

- All TYPICAL antipsychotics have **potent dopamine D2 receptor blocking action** (High D/5HT_{2A} affinity).
- **Atypical antipsychotics have 5-HT_{2A} blocking action** with NO major D2 blockade (High D/5HT_{2A} affinity - hence LESS extrapyramidal side effects).

Adverse Effects of Typical Antipsychotics

- **Low potency:** Chlorpromazine, thioridazine = non-neurologic side effects.
- **High potency:** Haloperidol, trifluoperazine = neurologic (extrapyramidal) side effects.
- **Extrapyramidal side effects** with timing of evolution:

Time	Effects
4 hours	Acute dystonia (MC in young men, girls < 10 years, esp. after IV/IM, muscle spasm, stiffness, oculogyric crisis); earliest appearing symptom Treat with centrally acting anti-cholinergics (Promethazine, Benhexol, Trihexphenidyl)
4 days	akinesia (Parkinsonian symptoms)
4 weeks	akathisia (MC side effect, restlessness with a compelling desire to move about but without anxiety)-rx with propranolol
4 months	Tardive dyskinesia (stereotypical oro-facial movements, Robbit syndrome) change to Clozapine

- **Anticholinergic** (maximum with thioridazine): dry mouth, blurred near vision, urinary retention, acute glaucoma in narrow angle patients.
- **Antiadrenergic:** sedation (maximum with chlorpromazine), postural hypotension, and sexual dysfunction.
- **Endocrine:** Dopamine receptor blocking → hyperprolactinemia → **galactorrhea, amenorrhea**.

- **Idiosyncratic reactions:** Cholestatic jaundice (chlorpromazine), agranulocytosis, skin rashes, urticaria, contact dermatitis, photosensitivity.
- **Neurolept malignant syndrome:** rigidity, myoglobinuria, autonomic instability, hyperpyrexia; treated with **dantrolene (DOC)** and **dopamine antagonists** (bromocriptine, amantadine).
- **Chlorpromazine:** Corneal and lens deposits/Cataracts and blue-grey skin pigmentation.
- **Thioridazine:** retinal deposits; hypotension.

Distinctive Features of Conventional Antipsychotics

- **Haloperidol:** It produces few autonomic effects, is less epileptogenic, DOES NOT cause weight gain, jaundice is rare. It is the **preferred drug for acute schizophrenia, Huntington's disease, Gille's de la Tourette syndrome**. High dose IV haloperidol may cause torsades de pointes.
- **Chlorpromazine:** In addition to psychiatry, it is also used in treating **nausea and vomiting, intractable hiccups, preanesthetic medication, skeletal muscle relaxation in tetanus**.

Distinctive Features of Atypical Antipsychotics

Clozapine

- It suppresses both positive and negative symptoms of schizophrenia (more preferred for negative symptoms).
- 1% risk of **agranulocytosis**, which requires weekly WBC count monitoring for first 6 months and then bi-weekly;
- Drooling of saliva (sialorrhea)
- Ileus/constipation
- Weight gain

Contd...

Contd...

Clozapine

- Myocarditis
- Hyperthermia
- New onset type 2 DM
- Hyperlipidemia
- Lowers seizure threshold.

- Olanzapine:** More effective than haloperidol in the treatment of negative symptoms of SZ. SE: **weight gain, new onset type 2 DM, hyperlipidemia; elevated serum alanine aminotransferase, sedation, agitation and hyperprolactinemia.**
- Quetiapine:** Eye examination to detect **cataracts**; weight gain; **sedation**
- Risperidone:** Hyperprolactinemia; decreased libido; amenorrhea
- Lurasidone:** Used for **acute decompensation of chronic schizophrenia, low incidence of weight gain/increased pids/prolonged QTc.** BUT extrapyramidal side effects like akathisia can occur.
- Drugs which **prolong QTc:** Thioridazine, Asenapine, Ziprasidone, lurasidone, Paliperidone, Quetiapine.

Depot antipsychotic

Long acting (depot) injectable antipsychotics available are **haloperidol; fluphenazine, flupenthixol; risperidone, aripiprazole, olanzapine ziprasidone.**

ANTIDEPRESSANTS**Classification of Antidepressants**

Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine (longest acting), Fluvoxamine (shortest acting), Paroxetine (most teratogenic), Sertraline, Citalopram, Escitalopram (most specific SSRI)
Tricyclic antidepressants: NA and Serotonin Reuptake Inhibitors	Imipramine, Nortriptyline (best tolerated), Amitriptyline, Desipramine, Protriptyline, Trimipramine, Clomipramine, Doxepin, Opipramol
Tetracyclic antidepressants	Amoxapine, Maprotiline, Mianserin
Selective Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	Duloxetine, Venlafaxine, Milnacipran
Noradrenaline reuptake Inhibitors (NARI)	Reboxetine
5-HT ₂ antagonists	Nefazodone, Trazodone

Contd...

Contd...

Dopamine and NA Reuptake Inhibitors

Bupropion

Melatonin receptor **agonist** Agomelatine and 5-HT_{2c} antagonist

Adverse Effects of Tricyclic Antidepressants

- Anticholinergic** dry mouth, tachycardia, blurred vision, urinary retention (careful in BPH), sexual dysfunction
- Antiadrenergic** sedation (desipramine less sedating), postural hypotension, sexual dysfunction
- Histamine H₁ receptor blockade** sedation, weight gain
- Cardiac:** conduction defects, cardiac arrhythmias (especially amitriptyline), seizures
- Other** seizures, rash, edema, leucopenia, and elevated liver enzymes.

Essential points about individual antidepressants

- SSRIs are the first choice drugs** for: Depression; OCD, gen anxiety disorder; panic disorder; PTSD; bulimia, premenstrual disorder.
- Adverse effects common to all SSRIs:** Headache, nausea, tinnitus, insomnia, nervousness, sexual dysfunction; **Cyproheptadine** prior to sexual activity may counter drug induced anorgasmia.
- Since SSRIs can affect platelet serotonin levels, **abnormal bleeding** can occur (sertraline and citalopram are safest when used with warfarin).
- Fluoxetine:** may cause **SIADH** causing hyponatremia in the elderly.
- Venlafaxine:** used in generalized anxiety disorder, ↑ BP.
- Bupropion:** causes minimal sexual side effects and seizure in bulimic patients; also used for **smoking cessation.**
- Citalopram:** **QT prolongation**, but NOT with escitalopram.
- Sertraline:** safe in acute MI or angina.
- Trazodone and nefazodone:** may cause **priapism.**
- Nefazodone** should NOT be given with **terfenadine, astemizole, or cisapride** - risk of **QTc prolongation**; risk of **hepatic failure** also.
- Tianeptine:** glutamatergic modulator
- Mirtazapine:** Noradrenergic and Selective Serotonergic Antidepressant (NaSSA); also used as anti-emetic and appetite stimulant.

Monoamine Oxidase (MAO) Inhibitors

- Nonselective** = Phenelzine, Tranylcypromine
- Reversible and selective inhibitor of MAO-A** = Moclohemide
- MAO-B selective** = Selegiline
- Mechanism:** MAO inhibitors irreversibly limit the activity of monoamine oxidase, increase the availability

of norepinephrine and serotonin in the synapse, and improve mood.

- Clinical use: atypical depression (third choice after SSRIs and TCAs), anxiety, hypochondriasis.
- Caution** with MAO inhibitors: **Hypertensive (hyperadrenergic) crisis** precipitated by ingestion of pressor amines in tyramine-containing foods (aged cheese, red wine) or β agonists - CHEESE reaction; **Phentolamine** is the **DOC** for cheese reaction.
- MAOIs + SSRIs or MAOIs + venlafaxine or SSRI's alone in high doses = potentially life-threatening drug-drug interaction, the '**serotonin syndrome**' = **Hyperthermia, Autonomic instability (delirium), Rigidity, Myoclonus, Seizures, ('HARMS')** and death. Stop offending medication. Give **serotonin antagonist** or **cyproheptadine**. **HENCE SSRIs should be started only 14 days after stopping MAOIs.**

Antidepressants effective in other conditions are:

- OCD (clomipramine)**
- Enuresis (imipramine)**
- Psychotic depression (amoxapine)**
- Reduction of craving in cocaine withdrawal (desipramine)**
- Amitriptyline (migraine prophylaxis)**
- Antipruritic: topical doxepin**
- Bupropion:** used for smoking cessation
- Duloxetine:** urinary stress incontinence

MOOD-STABILIZING DRUGS**Lithium**

- Lithium (Li) is small **monovalent cation**; Li is used as its **carbonate salt** (less hygroscopic and less gastric irritant); it is **converted into chloride in the stomach**; Li therapy started by **John FJ Cade.**
- MOA: **Li inhibit hydrolysis of inositol-1-phosphate.**
- Side effects of Lithium**
 - Leukocytosis**
 - Postural tremor** (MC side effect, treat with propranolol)
 - Hypothyroidism**
 - Nephrogenic diabetes insipidus** (NDI, thirst and polyuria); DOC is **amiloride.**
 - Fatigue, weight gain, acne, folliculitis.
 - Rare side effects: **Neurotoxicity, renal toxicity, hypercalcemia, ECG changes (T wave flattening/inversion), nephrotic syndrome, pseudotumor cerebri, teratogenic (Ebstein anomaly of tricuspid valves).**
 - 'LITHIUM' = Leukocytes Increased Tremors hypothyroidism Increased Urine (NDI) Mom be careful (teratogenic)**

Uses of Lithium are

- In treatment of **acute mania** and **prophylaxis of bipolar mood disorder** (Harrison's 19th/2718).
- Other uses are in **Cluster headache; Cancer chemotherapy linked agranulocytosis and neutropenia** (Li increases leukocyte count); **SIADH; Cyclical vomiting; Huntington's chorea.**
- Lithium has anti-suicidal effect.

Pharmacokinetics of Lithium

- Lithium is well-absorbed orally; steady state plasma concentrations are reached in 7 days; its t_{1/2} is 24 hours; it is **NEITHER** protein bound nor metabolized and is excreted unchanged exclusively by the kidneys.
- It has **low therapeutic index.**
- Starting dose:** 300 mg bd or tid.
- Serum Blood lithium levels
 - For treatment of **acute mania** = 0.8-1.1 mEq/l
 - For prophylaxis of **bipolar disorder** = 0.5-0.8 mEq/l
 - Serious **toxicity** occur with > 1.5 mEq/l.
- Blood level is increased** by diuretics (thiazides and potassium sparing diuretics, but NOT loop diuretics), ACE inhibitors, tetracyclines, NSAIDs, hyponatremia.
- Blood level is decreased** by bronchodilators (theophylline, aminophylline), verapamil, carbonic anhydrase inhibitors, osmotic diuretics (urea, mannitol), sodium bicarbonate.
- Acute toxicity:** treat with induced emesis and gastric lavage; if levels > 4 mEq/l - treatment of choice is **hemodialysis.**
- Lithium should be stopped **24 hours** before major surgery.
- Serum Lithium level should be checked earliest after **5 days** of constant dosing.

Alternatives to Lithium

- Sodium Valproate:** DOC for rapid cyclers
- Lamotrigine:** for long-term maintenance of **bipolar disorder.**
- Atypical antipsychotics:** Olanzapine, aripiprazole, quetiapine, risperidone are also FDA approved for control of **acute mania.**
- Carbamazepine:** An anti-epileptic, which is also used for acute mania and prophylactic therapy.

ANTI-ANXIETY DRUGS**Benzodiazepines (BZDs)**

- These are the MC used anxiolytic drugs.
- Oxazepam, lorazepam, alprazolam, tofisopam and diazepam** are used for short lasting anxiety states; **chlordiazepoxide** for chronic anxiety states (**propranolol** is indicated for performance anxiety).
- Newer Non BZD hypnotics:
 - Zolpidem, Zaleplon, Eszopiclone** - useful in management of sleep disorders (insomnia).

- **Azapirones:** *Buspirone, gepirone and isapirone* partial agonists of 5-HT_{1A} receptors and decrease release of serotonin; *no sedation, anticonvulsant or muscle relaxant properties; ineffective* in acute anxiety.

More about BZDs

- **BZDs with active metabolites:** Alprazolam, Buspirone (non-BZD), Chlordiazepoxide, Diazepam, Flurazepam (prodrug, but metabolites are active) - 'ABCDeF'
- **Side effects of BZDs:** Disinhibition, ataxia, dysarthria, nystagmus, and delirium; Paradoxical agitation, anxiety, psychosis, confusion, mood lability, and anterograde amnesia
- **BZD Overdosage** results in respiratory depression, hypotension, shock, coma, and death. **Flumazenil** is a BZD antagonist.

Varenceline

- Varenceline is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment.
- Begin varenceline dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin varenceline dosing and then quit smoking between days 8 and 35 of treatment.
- **Starting week:** 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7.
- **Continuing weeks:** 1 mg twice daily for a total of 12 weeks (2.1).
- **Neuropsychiatric side effects:** Changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

PSYCHOANALYSIS

Father of psychoanalysis = Sigmund Freud (1856-1939). Born in Frieberg (now called Příbor in the Czech republic); died in London. The central approach of psychoanalysis is to slowly uncover experiences that are repressed in the unconscious mind and integrate them into the patient's personality.

Freud's Topographic Theory of Mind

- **The Conscious:** uses SECONDARY PROCESS thinking (e.g. logical, time-oriented, mature) based on reality principle.

- **The Preconscious:** Contains memories that are not immediately available, but can easily become conscious with the focusing of attention (e.g. your phone number).
- **The Unconscious:** This component of mind contains repressed ideas and feelings; uses PRIMARY PROCESS thinking.
- The ultimate goal of Freudian psychoanalysis is to make the patient aware of what is hidden in his/her unconscious.



Fig. 28.1: Sigmund Freud

Structural Theories of Mind

- **Id**
 - Original state of human mental apparatus with which a newborn baby is born and is controlled by PRIMARY PROCESS thinking (*unorganized, non-logical*); contains instinctual, sexual and aggressive drives, acts in concert with the pleasure principle and is not influenced by external reality; operates almost completely on an **unconscious level**.
- **Ego**
 - Begins to develop immediately after birth; *guided by the reality principle; predominantly conscious* though some parts (ego defense mechanisms) are unconscious. The ego is the seat of conscious, intellectual, self-preservative and defensive functions of mental apparatus.
- **Superego**
 - Developed by approximately **6 years of age**, an unconscious subdivision of mental apparatus that develops from the ego; a/w **conscience and morality**.
- **Oedipus complex:** Repressed sexual feelings of a **child for the opposite sex parent**, (3-5 years old boys toward the mother) accompanied by rivalry with same-sex parent. First described by Freud.

Techniques Used to Recover Repressed Experiences

- **Free Association:** (i.e. the patient lies on a couch in a reclined position facing away from the therapist and says whatever comes to the mind); the therapist interprets the information.
- **Interpretation of dreams:** As representations of conflict between fears and wishes (satisfaction of unconscious instinctual impulses)
- **Analysis of transference reactions:** (i.e. the patients reactions to the therapist) to examine important past relationships.
- **Analysis of resistance:** (i.e. blocking unconscious thoughts from consciousness because the patient finds them unacceptable).

Transference and Counter-transference

These are phenomena that occur *during psychoanalysis* as well as sometimes in ordinary physician-patient relationships.

Transference

- Unconscious re-experiencing of feelings about parents or important life figures in *Patient's* life in his current relationship with the therapist
- **PP:** A 35-year-old man with a mother who often disappointed him becomes angry when his physician attempts to terminate his consultation with him

Counter-transference

- Unconscious re-experiencing of feelings about parents or important life figures in *Therapist's* life in his current relationship with the patient
- **Example:** A physician becomes annoyed with a noncompliant patient who reminds him of his obstinate son

Ego Defense Mechanisms

Ego defence mechanisms are coping styles that are employed automatically and most often unconsciously to protect the anxiety that arises when who we really are (our unconscious 'id') comes into conflict with who we would like to be (our unconscious 'superego'). (Ex: 'A man maybe unconsciously attracted to another man; but at a conscious level he may find this attraction completely unacceptable; To defuse this anxiety - he may refuse to admit to himself that he is attracted to another man (ego defence here is - denial) or he may project his attraction onto somebody else and berate him for being 'gay' (ego defence here is - projection)).

Mature Ego Defense Mechanisms are:

- ALtruism
- ANticipation
- Humor
- ASceticism
- SUBlimation
- SUPpression.

Mnemonic: 'ALAN HAS SUSU I'

Stages of Psychosexual Development

Phase	Disorder resulting from fixation at this phase
Oral phase (birth to 1 year)	Depression, narcissism
Anal phase (1-3 years)	OCD
Phallic phase (3-5 years)	Oedipus complex; Pedophilia
Latent phase (6- adolescence/12 years)	
Genital phase (puberty/13 years onwards)	Gender confusion

Behavioral and Cognitive Therapies

Behavioral and cognitive therapies are based on learning theory (i.e. relieving the patient's symptoms by altering the behavior and thinking patterns).

Therapy and Common Use with Clinical Examples

Systemic Desensitization

- Treatment of phobias

PP: The classic, fear of flight example! A woman who is scared of flights is taught relaxation techniques and then shown photos of an airplane and then taken into the airport few times, then she is exposed to toy planes and finally she takes a airplane ride.

Aversive conditioning

- Treatment of paraphilias or addictions (drinks/smoking)

PP: A 40-year-old man with pedophilia is given a small electric shock each time he is shown a picture/videotape of children. Later he feels uncomfortable around children and avoids them.

Flooding and implosion

- Treatment of phobias

PP: A woman who is afraid of flights agrees to take a 9-hour flight to Frankfurt.

Taken economy

- To increase positive behavior in mentally retarded persons

PP: A 25-year-old mentally retarded man is given a token each time he shaves. He can exchange tokens for sweets at the hospital store and then begins to shave every day.

Contd...

Contd...

Cognitive behavior therapy (CBT)

- To treat mild to moderate depression, somatoform disorders, eating disorders.

Stages of CBT = Pre-contemplation, Contemplation, Preparation, Action, Maintenance, Termination/relapse

PP: A 40-year-old woman with depression is thought to replace each self-downgrading thought with a mental image of success and praise

Biofeedback

- To treat hypertension, migraine, asthma, chronic pain
- PP:** A 55-year-old man with hypertension has his BP measured regularly. He is told the readings each time and taught mental relaxation techniques to decrease BP

- **Group therapy:** Used for people with a *common problem* (e.g. alcoholics, rape victims, substance abusers). **Alcoholics Anonymous** is based on group therapy. Groups of usually 8-10 people meet weekly for 1-2 hours. The therapist facilitates and observes the patients' interpersonal relationships, *but has little input*.
- **Family therapy:** Used in *behavioral problems in children, family conflict, eating disorders and substance abuse*.
- **Marital therapy:** To explore and resolve communication problems, psychosexual problems and differences in values.

ELECTROCONVULSIVE THERAPY

- Started as electroshock therapy by Cerletti and Bini in 1938.
- **Indications**
 - Major **severe depression with suicidal risk** (*most important indication*).
 - Others: Catatonic SZ; Severe SZ (acute) and mania not responding to drug treatment; Patients not eating or drinking (e.g. in anorexia nervosa).
 - Elderly patients and depression +somatization patients are **LESS** likely to respond to ECT
- **Contraindications**
 - Most important is **raised intracranial tension**
 - Others are recent MI, recent stroke, crescendo angina, retinal detachment, pheochromocytoma.
- **Technique**
 - Informed **consent** is necessary either from the patient or from the guardian.
 - Before each treatment patient should be on empty stomach for 8 hours.
 - Direct ECT (rare) is given in the absence of muscle relaxants or general anesthesia.

- Modified ECT is given with drug induced muscle relaxation and general anesthesia.
- This is given through electrodes placed bitemporally (bilateral) or with both on the non-dominant hemisphere.
- The principle is to give an electric shock that is *greater than the seizure threshold*.
- **Side-effects**
 - **Anterograde** amnesia: **most common**; impairment of new memory retention after course of ECT. Typically resolves in 1-3 weeks after ECT.
 - **Retrograde** amnesia: **Most serious** adverse effect of ECT. Memories for 4-12 weeks before the episode of ECT are forgotten- takes longer to resolve and may be persistent (i.e. these memories may be permanently forgotten).
- **Mechanism of Action**
 - Not clearly known but there is down-regulation of beta-adrenergic receptors (similar to what happens with antidepressants).

CULTURE-BOUND SYNDROMES

- **Amok:** is a response to humiliation involving initial brooding followed by a period of altered consciousness characterized by uncontrollable (usually **homicidal and sometimes suicidal**) **rage**, for which the subject has no subsequent memory. '**Run amok**' is also seen in chronic **marijuana (cannabis) abuse**.
- **Ataque de nervios:** consists of a grief reaction characterized by fluctuating conscious level (often with subsequent amnesia), crying, shouting, trembling and difficulty in moving limbs. Hyperventilation may be important in precipitating the symptoms.
- **Brain fog:** is characterized by **concentration difficulties, vague somatic complaints and depressed mood**.
- **Dhat syndrome:** seen in **Indian** subcontinent, characterized by complaint of passage of 'dhat' in urine, multiple somatic symptoms, asthenia, anxiety, **sexual dysfunction**. 'Dhat' is a whitish discharge passed in the urine and is believed to be semen by the patient, and that its loss will lead to weakness and sexual dysfunction.
- **Koro:** involves intense anxiety centred on the belief that **one's genitalia are retracting** and that their disappearance will result in death.
- **Latah:** is a response to intense stress characterized by altered consciousness, hypersuggestibility, mimicry (including echolalia and echopraxia).
- **Piblokto (arctic hysteria):** The affected person is often a **female who screams, tears off her clothes, and throws**

herself on ice in extremely cold conditions. She may imitate the cry of a bird or animal. The episode usually lasts for 1-2 hours followed by amnesia for the events. It is probably a type of dissociative disorder.

- **Wihitigo:** The affected person believes that he has been transformed into a **wihitigo, a cannibal monster**, especially during times of starvation.
- Other culture bound syndromes seen in India include **Sucht-bai** (purity mania), ascetic syndrome, nuptial psychosis and **jhunjhuni**.

Durations to Define Few Psychiatric Illnesses

Illness		Minimum duration
Mania		7 days (1 week)
Major depression		2 weeks
PTSD		1 month
Panic disorder		1 month
Insomnia		1 month
Generalized Anxiety Disorder		6 months
ADHD		6 months
Schizophrenia (DSM IV)		6 months
Schizophrenia (ICD-10)		1 month

Neurotransmitter Changes in Diseases

Disorder	Neurotransmitter changes
Alzheimer's disease	↓ ACh
Schizophrenia	↑ Dopamine

Contd...

Specific test or measure	Uses and characteristics
NEUROENDOCRINE MEASURES	
• Dopamine (homovanilic acid)	↑↑ in schizophrenia and other conditions involving psychosis; ↓↓ in Parkinson's disease and depression.
• Norepinephrine (VMA and MHPG)	VMA elevated in pheochromocytoma; MHPG ↓↓ in severe depression
• Serotonin (5-HIAA)	↓↓ in severe depression, impulsiveness, violence, fire setting, Tourette syndrome, alcohol abuse and bulimia
• Dexamethasone suppression test (DST)	Used to predict which patients will respond well to treatment with antidepressant agents or to ECT (i.e. those with a positive DST result, defined as reduced suppression of cortisol after test dose with dexamethasone)
• Serum prolactin levels	↑ in seizures (postictal period) and during treatment with antipsychotics.
OTHER TESTS	
• Sodium amobarbital ('truth serum') Interview	Relaxes patients with conditions such as conversion disorder, mute psychotic states and dissociative disorders so that they can express themselves during an interview
• Intravenous administration of sodium lactate or Inhalation of CO₂	Used to diagnose panic disorder because either treatment can provoke a panic attack in an affected patient

Contd...

Contd...

Disorder	Neurotransmitter changes
Depression	↓ NE, ↓ serotonin (5-HT), ↓ dopamine
Anxiety	↑ NE, ↓ GABA, ↓ 5-HT
Parkinson's disease	↓ dopamine, ↑ 5-HT, ↑ ACh
Huntington's disease	↓ GABA, ↓ ACh, ↑ dopamine

TESTS IN PSYCHIATRY

Types of Diagnostic Tests in Psychiatry

- **Objective test:** An objective test is based on *question with right or wrong answers that are easily scored and statistically analyzed*.
- **Projective test:** A projective test requires the *subject and the examiner to interpret the questions*. Responses are assumed to be based on the subject's motivational state and defense mechanisms.
- **Intelligence test:** Intelligence is defined as the *ability to understand abstract concepts; to reason, to assimilate, recall, analyze and organize information; and to meet the special needs of new situations*.
- **Achievement tests:** These evaluate how well an individual has mastered **specific subject areas**.
- **Personality tests:** These are used to **evaluate psychopathology** and **personality** characteristics.
- **Neuropsychological tests:** These are used to **assess general intelligence, memory, reasoning, orientation, perceptuomotor performance, language function, attention and concentration in patients with suspected neurological problems**.

Contd...

Specific test or measure	Uses and characteristics
• Galvanic skin response (GSR)	Identifies level of stress as shown by arousal of the sympathetic nervous system; measures increased sweat gland activity that causes decreased electric resistance of the skin; used in polygraph (lie detection test)
• Serum Creatine Phosphokinase	Neurolept malignant syndrome (markedly increased levels)

Psychological and Neuropsychological Diagnostic Tests

Test	Uses and characteristics
Intelligence tests (IQ tests)	
• Wechsler Adult Intelligence Scale Revised (WAIS-R)	11 subsets (6 verbal and 5 performance)
• Wechsler Intelligence Scale for Children revised (WISC-R)	Used to test intelligence in children 6-16.5 years of age
• Stanford-Binet test	IQ = Mental age/Chronological age X 100
Achievement tests	
• Wide-Range Achievement Test (WRAT)	Used clinically to evaluate arithmetic, reading and spelling skills
• Peabody Individual Achievement Test	Used in school systems to evaluate achievement in specific subject areas
Personality tests	
• Minnesota Multiphasic Personality Inventory (MMPI-20)	Objective test in which patients answer 56 true or false questions about themselves
• Rorschach Inkblot test	Projective test in which patients interpret 10 bilaterally symmetric inkblot designs ; used to identify thought disorders and defense mechanisms
• Sentence completion test (SCT)	Projective test in which patients complete sentences (e.g. I would most like to
• Thematic Apperception Test (TAT)	Projective test in which patients create scenarios based on 30 pictures of ambiguous situations ; the scenarios are used to evaluate unconscious emotions and struggles
Neuropsychological tests	
• Halsted-Reitan Battery (HRB)	Used to detect and localize brain lesions ; Test includes <ul style="list-style-type: none"> • Trail making tests part A and B • Halsted category test (includes counting factor; spatial positioning reasoning factor; proportional reasoning factor; incidental memory factor) • Tactual performance test • Seashore rhythm test • Speech Sounds perception test • Finger oscillation test • Sensory Perceptual examination • Lateral dominance examination
Luria-Nebraska Battery (LLNB)	Used to determine left or right cerebral dominance
Bender Gestalt Test	Visual-Motor test; used to screen visual and motor ability through reproduction of designs; used to detect organic brain damage

CHANGES IN DSM-V

DSM (Diagnostic and Statistical Manual of Mental Disorders) is the manual used by clinicians and researchers to diagnose and classify mental disorders. The American Psychiatric Association (APA) published **DSM-5 in 2013**.

General Changes

- The **5 axes system** (multi-axial system) has been **removed**
- Restructured Order of Chapters: The order of **chapters (20 in all)** in the DSM-5 is different from past editions.
- The term mental retardation is replaced with **intellectual disability**.

Communication Disorders

These include

- **Language** disorder (which combines DSM-IV expressive and mixed receptive-expressive language disorders)
- **Speech sound** disorder (a new name for phonological disorder)
- Childhood-onset fluency disorder (a new name for **stuttering**)
- **Social (pragmatic)** communication disorder, a new condition for persistent difficulties in the social uses of verbal and nonverbal communication.

Autism Spectrum Disorder

This term now encompasses the previous DSM-IV **autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder** not otherwise specified.

Specific Learning Disorder

This combines the DSM-IV diagnoses of

- **Reading** disorder,
- **Mathematics** disorder,
- Disorder of **written expression**, and
- Learning disorder not otherwise specified.

Motor Disorders

These are included in the DSM-5 neurodevelopmental disorders chapter and include: developmental coordination disorder, stereotypic movement disorder, Tourette's disorder, persistent (chronic) motor or vocal tic disorder, provisional tic disorder, other specified tic disorder, and unspecified tic disorder.

Schizophrenia

The DSM-V changes with regard to Schizophrenia have been already mentioned under 'Diagnostic Criteria' under Schizophrenia topic.

Anxiety Disorders

The DSM-5 chapter on anxiety disorder **no longer includes obsessive-compulsive disorder** (which is included with the obsessive-compulsive and related disorders) or **posttraumatic stress disorder and acute stress disorder** (which is included with the trauma- and stressor-related disorders).

Obsessive-Compulsive and Related Disorders

New chapter in DSM-5 is on obsessive-compulsive and related disorders; new disorders include:

- **Hoarding** disorder
- **Excoriation** (skin-picking) disorder
- **Substance-/medication-induced** obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition.

Trauma- and Stressor-Related Disorders

- Acute Stress Disorder
- Adjustment Disorders
- Posttraumatic Stress Disorder
- Reactive Attachment Disorder

Gender Dysphoria

Gender dysphoria is a new diagnostic class in DSM-5.

Major and Mild Neurocognitive Disorder

The DSM-IV diagnoses of **dementia and amnesic disorder** are subsumed under the newly named entity **major neurocognitive disorder (NCD)**.

Anesthesiology

HISTORY OF ANESTHESIA

Oliver Wendell Holmes	Coined the term ' anesthesia '
John Lundy and Ralph Waters	Coined the term ' balanced anesthesia '
August Bier	Father of spinal anesthesia and intravenous regional anesthesia
WTG Morton	Father of modern anesthesia He demonstrated effects of Ether in Boston on 16th October 1846 (16th October—World Anesthesia Day, World Ether Day!)
Joseph Priestley	Discovered nitrous oxide in 1772
Horace Wells	First used nitrous oxide as anesthetic agent in 1845
Archie Brain	Designed Laryngeal Mask Airway (LMA)
MacEwen	First performed endotracheal intubation
IW Magill	Father of endotracheal anesthesia ; developed red rubber endotracheal tube and Magill forceps
(Jack) Michenfelder and Albert Faulconer	Father of neuroanesthesia
Simpson	First to use chloroform
Gwathmey and Boyle	Invented anesthesia machine
Woodbridge	Pin Index safety system

AIRWAY ASSESSMENT

- **Mallampati criteria (modified Samson-Young classification)**
 - Based on **structures visible on full opening of the mouth**; **grades 3 and 4 suggest difficult intubation**
 - Class I = Tonsillar pillars, soft palate and uvula visible
 - Class II = Pillars obscured but soft palate and uvula visible
 - Class III = Only soft palate visible
 - Class IV = Soft palate is not seen
- **Modified Cormack and Lehane grading**
 - Describes **the best view of the larynx seen at laryngoscopy**; **grades IIb; II and IV suggest difficult intubation**
 - Class I = Vocal cords (glottis) are visible
 - Class II = Vocal cords are only partially visible
 - Class IIa = Only part of the glottis is visible
 - Class IIb = Only the arytenoids are visible
 - Class III = Only epiglottis is seen (no glottis)
 - Class IV = Only soft palate seen
- **Thyromental distance (Patil et al.)**
 - With the head fully extended, the distance between the **bony point of the chin** and the **prominence of the thyroid cartilage** is measured
 - A distance of **< 6.5 cm** suggests **difficult intubation**
- **Sternomental distance (Savva's test)**
 - With the head fully extended, the distance from the **sternum** to the **tip of the mandible** is measured
 - A distance of **≤ 12.5 cm** predicts **difficult intubation**

Contd

Contd...

- **Protrusion of the mandible (Cadler test)**
 - This is an indication of the **mobility of the mandible**
 - If the **patient is able to protrude the lower teeth beyond the upper incisors** intubation is usually straightforward
- **Wilson's risk score**
 - Scores are assigned from 0-2 for **weight, head and neck movement, jaw movement, receding mandible, buck teeth**
 - **Score of 3 or more** predicts **difficult intubation**
- **Prayer sign**
 - Inability to place **both palms flat together** suggest **difficult intubation**. It is probably a reflection of generalized joint and cartilage immobility limiting atlantoaxial and cervical extension. MC in **diabetics**
- **Submandibular compliance**
 - Submandibular space is the area into which the soft tissues of the pharynx must be displaced to obtain clear view of the airway; anything that **limits submandibular compliance—Ludwig's angina, radiation scoring, burns, previous neck surgery**—can cause difficult intubation
- **Delikan's warning sign**
 - This test the extension of the neck at the atlanto-occipital joint which is important for intubation

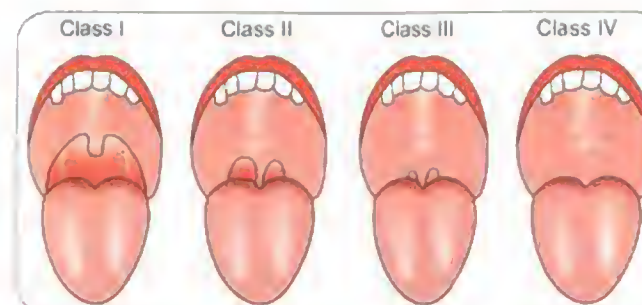


Fig. 29.1: Mallampati classification or test of oral opening

ENDOTRACHEAL TUBES

- **Tube Design**
 - Endotracheal tube has a **preformed curve** to approximate the anatomical curve of the airway—radius of curvature varies from **12–16 mm**.
 - The tube consists of the **distal/tracheal end** and the **proximal/machine end**. The proximal end received the **tapered 15 mm male connector** for attachment to the breathing system.
 - The distal end has a **bevel facing to the left** to facilitate visualization of the tube passing between the vocal cords.
 - The angle between the long axis of the tube and the bevel (**angle of the bevel**) is **38 degrees**.
 - The **Murphy eye** is a side vent near the distal end of an ETT. It was created to prevent complete respiratory obstruction in the event that the open end of the ETT were to become sealed by contact with the tracheal wall or occluded by a mass or mucus plug.
- **Material of the tube**
 - Historically ETT were made of **red rubber**, but NOW **Poly Vinyl Chloride (PVC)** tubes are used.
 - Other materials used are **polyurethane** and **silicone rubber** (polymethylsiloxane).
 - The material used for the ETT is tested for its non-irritant nature by implantation in the **paravertebral muscle of anesthetized rabbits** for **70–144 hours** after which the implant sites are assessed for evidence of inflammation. The number marked on the tube '**Z79-IT**' denotes that this implant test has been done.
 - Ideal ETT material should be **transparent** and **radio-opaque**.
- **Cuff**
 - Cuff seals the space between the tube and wall of trachea and prevents gas leaks during positive pressure ventilation and also prevents aspiration.
 - Cuffs can be made of rubber, PVC or polyurethane.
 - **Silicone and red rubber** cuffs = High pressure and low volume
 - **pVC** cuff (now used) = Low pressure and high volume (small **p** = low pressure; high volume = capital **V**).
 - **Pilot balloon** is located close to the inflation valve and indicates the distension of the cuff.
 - Cuff is inflated with air; **cuff pressure should be < 30 cm H₂O**, so that it is below the tracheal capillary perfusion pressure (35 mm Hg) to prevent tracheal mucosal ischemia.
 - **Traditional teaching** says that **in children < 8 years, uncuffed tubes are used**—HOWEVER, newer evidence has shown that with Microcuff tubes, cuffed ETT may be used in all ages.

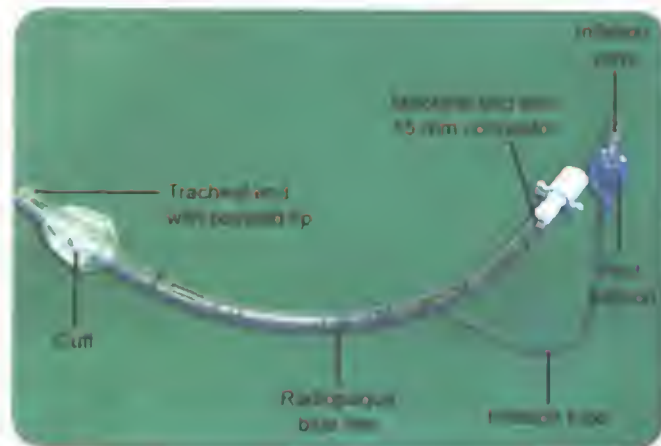


Fig. 29.2: Parts of an endotracheal tube



Fig. 29.3: Bevel and Murphy eye

Special Types of Endotracheal Tubes (ETT)

RAE tubes (Ring, Adair, Elwyn tubes)

These are special ETTs with a **preformed (premolded) bend**; these are designed with the intention to allow easy surgical access for ENT and oral surgery.

- **'South' facing or 'south-polar' or 'Oral RAE' ETT:** Here the tube emerges from the patient's mouth and faces the patient's feet, thus giving good access to nasal passages for the ENT surgeon to work.
- **'North' facing or 'north-polar' or 'Nasal RAE' ETT:** Here, the tube emerges from the patient's mouth and faces the patient's top, thus giving good access to the surgeon for dental work.

- **Flexometallic tubes:** Aka 'armored' tubes, 'reinforced' tubes or 'spiral embedded' tubes. They have a spiral wire embedded in the tube wall to prevent easy kinking. Used in prone position, head and neck surgeries, through tracheostomy stoma and in submental intubations.

- **'Double lumen' tubes:** Used for thoracic surgery (where ventilation of only one lung is required, e.g. during esophagectomy, one may choose not to ventilate the lung to provide better surgical access to the esophagus).
- **Micro-laryngeal tubes:** For micro-laryngeal surgery to enable improved surgical access in micro-laryngeal surgery.
- **Laryngectomy tube:** It has a distal 'U-shaped bend' to allow insertion through tracheostomy in patients with laryngectomy.
- **LITA tube:** Laryngotracheal Instillation of Topical Anesthetic tube; it has a specially designed lumen for spray application of topical anesthetic.
- **Esophageal tracheal combitube:** Double lumen device that can function as either an endotracheal device or an esophageal obturator; it can be used blindly in emergency medical management.
- **Laser tubes:** These laser-resistant tubes can be used with CO₂ and KTP lasers. Examples are: *Laser Jet* (Mallinckrodt tube); *Laser shield II*; *Sheridan* tube; *Norton* tube. Of these the ONLY 'laser proof' (meaning—it will not catch fire) is the Norton tube.



Fig. 29.4: RAE (Ring, Adair, Elwyn) south tube for oral intubation

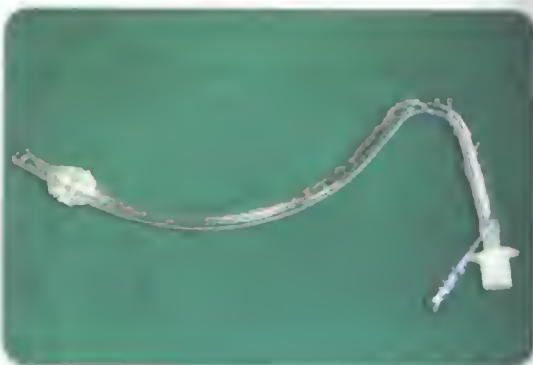


Fig. 29.5: RAE north tube for nasal intubation

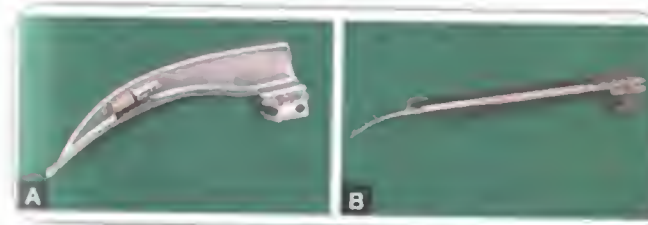
Size of Endotracheal Tube

Specified according to internal diameter in 0.5 mm increments.

Premature (< 1.5 kg)	2.5–3 mm
Premature (1.5–25 kg)	3 mm
Neonate	3.5 mm
1 year	4 mm
2–3 years	4.5 mm
Children > 2 years	(Age in years/4) + 4 mm (uncuffed tube); for cuffed tube use (+ 3.5 mm)
Adult male	8–8.5 mm
Adult female	7–8 mm

LARYNGOSCOPE

- **First direct laryngoscopy** was performed in 1895 by **Alfred Kristein**; BUT use of the direct laryngoscope for endotracheal intubation was popularized by **Sir Robert Macintosh** and **Sir Ivan Magill**.
- Size of laryngoscope ranges from **size 000 to size 5**.
- **Fiberoptic laryngoscope** has green circular band in the handle and a green dot in the heel of the blade.
- Types of laryngoscope blades:
 - **Macintosh:** Standard curved blade; MC used in adults.
 - **Miller:** Straight blade; used in children.
 - **McCoy:** Modified Macintosh blade in which the tip can be flexed by 25 mm by pressing a lever.
 - **Polio:** Modified Macintosh blade where the angle between the handle and blade is more obtuse (135 degrees instead of the usual 90 degrees).
 - **Flexiblade:** Can be flexed also.



Figs 29.6A and B: Different types of laryngoscope blades: A. Macintosh; B. Miller

Technique of laryngoscopy/intubation

- During intubation, there should be extension at atlanto-occipital joint and flexion at cervical spine—'**sniffing the morning air position** or **Magill's position**'.

- Patient's mouth is fully opened with index finger and thumb of right hand in a scissor action.
- The **Laryngoscope** is held in the **Left hand** and the blade introduced along the **right side of the patient's mouth** displacing the tongue to the left (**Both right and left handers MUST** hold the laryngoscope in their left hand only!!).
- If the laryngeal view is not good, the '**BURP**' maneuver can be used—**backward, upward and rightward pressure** (on the thyroid cartilage) by an assistant to push the laryngeal structures into the line of sight.
- '**DO NOT**' lever the laryngoscope blade on the teeth or the gums—you will break the patient's teeth!
- **Cricoid pressure** applied by assistant during intubation will help in visualizing the airway/vocal cords.

ENDOTRACHEAL INTUBATION

- During intubation, there should be **extension at atlanto-occipital joint and flexion at cervical spine**—'**sniffing the morning air position**'.
- Patient's **mouth is fully opened** with index finger and thumb of **right hand** in a scissor action.
- The **Laryngoscope** is held in the **Left hand** and the blade introduced **along the right side of the patient's mouth** displacing the tongue to the left (**Both right and left handers MUST** hold the laryngoscope in their **left hand** only!!)

Checking for correct tube position

- **Quantitative waveform Capnography (best method):** A sustained CO₂ waveform (end tidal pCO₂ > 30 mm Hg) for 3–5 consecutive breaths confirms that endotracheal tube is placed in trachea; < 0.2% CO₂ in exhaled air indicates esophageal intubation.
- Auscultation for **bilateral breath sounds**
- Symmetrical bilateral **chest inflation**
- Condensation of water in the tube lumen (**breath fogging**)
- Characteristic **feel** of the reservoir bag
- **Direct visualization** by laryngoscope
- **Esophageal intubation detector:** Easy plunger withdrawal suggests correct endotracheal tube placement; plunger resistance suggests esophageal tube placement.
- **Esophageal detector device:** Complete bulb reinflation suggests correct tube placement; incomplete bulb reinflation suggests esophageal placement.
- **FENEM CO₂ detector:** (colorimetric method): If endotracheal tube is **correctly placed**, CO₂ in exhaled air changes the color of indicator strip from **purple to yellow**.

Nasal (Nasotracheal) Intubation

- For nasal intubation 3 cm is added to length of oral tube.
- Used *very rarely* these days for certain procedures (e.g. Le Fort I osteotomy).
- **MC** complication is **epistaxis**.
- **Contraindication** to nasotracheal intubation are
 - Bleeding disturbances (coagulopathies or on anticoagulants)
 - Nasal pathology (epistaxis, deviated septum, polyps, infections)
 - Basal skull fractures
 - Facial trauma: Midfacial fractures including maxillofacial fractures.
 - In patients with apnea
 - CSF leakage/CSF rhinorrhea
 - Chronic sinusitis
 - Nasal stenosis

Congenital syndromes a/w difficult endotracheal intubation

- **Trisomy 21** (large tongue, small mouth)
- **Goldenhor** (oculoauriculovertebral anomalies)
- **Klippel Fiel** (fused cervical vertebrae—rigid neck)
- **Pierre Robin** (large tongue, small mouth)
- **Treacher Collins** (mandibular dysostosis)
- **Turner syndrome**

LARYNGEAL MASK AIRWAY (LMA)

- The LMA is a **supraglottic airway device** developed by **Dr Archi Brain**.
- LMA consists of a **12 mm inner diameter flexible shaft** connected to a silicone rubber mask that seals with the airway in the hypopharynx.
- When correctly inserted, the **distal tip** of the cuff should be against the **upper esophageal sphincter** (cricopharyngeus muscle), the **lateral edges** rest in the **piriform sinuses** and the **proximal end** seats under the base of the tongue.

Types of LMA

- The **LMA Classic** is the original **reusable** design.
- The **LMA Unique** is **disposable**, making it **ideal for emergency and prehospital settings**.
- The **LMA Fastrach**, an **intubating LMA (ILMA)** is designed to serve as a conduit for intubation. Although most LMA designs can serve this purpose, the LMA Fastrach has special features—an **insertion handle**, a **rigid shaft with anatomical curvature**, and an **epiglottic elevating bar** designed to lift the epiglottis

as the ETT passes. These *increase the rate of successful intubation* and *do not* limit the size of the endotracheal tube (ETT).

- The **LMA Flexible** has softer tubing. It is **not** used in the emergency setting.
- The **LMA ProSeal** has the addition of a **channel for the suctioning of gastric contents**. It also allows for **50% higher pressures** without a leak. However, it **does not permit blind intubation** and is not currently used in the emergency setting.
- The **LMA Supreme** which is a newer design is similar to the ProSeal and has a **built-in bite block** and a **high volume/low pressure cuff**.
- The **LMA CTrach** inserts like the LMA Fastrach and has built-in **fiberoptics** with a **video screen** that affords a direct view of the larynx.

Indications for LMA

- As **acceptable alternative to mask anesthesia** in the OI.
- As **acceptable alternative to intubation** for airway management in the cardiac arrest patient (Class IIa).
- **Used for short procedures** when endotracheal intubation is not necessary.
- After failed intubation, the **LMA can be used as a rescue device**.
- Useful in the **prehospital setting by emergency medical technicians**.
- LMA can be used as a **conduit for intubation (ILMA—intubating LMA - LMA Fastrach)**.

Contraindications for LMA

Absolute

- Cannot open mouth
- Complete upper airway obstruction

Relative contraindications (in elective setting)

- Increased risk of **aspiration**
- Prolonged bag-valve-mask ventilation
- Morbid obesity
- Second or third trimester pregnancy
- Patients who have not fasted before ventilation
- Upper gastrointestinal bleed
- Suspected or known abnormalities in supraglottic anatomy
- Need for high airway pressures

Complications of LMA Include

- **Aspiration** of gastric contents (Unlike the cuffed endotracheal tube, LMA does NOT protect the air-

way from aspiration of gastric contents if regurgitation occurs).

- Local irritation; Upper airway trauma; Pressure-induced lesions, nerve palsies; mild sympathetic response.

LMA size	Patient weight (Kg)
1	> 5
1.5	5–10
2	10–20
2.5	20–30
3	30–50
4	50–70
5	70–100
6	> 100

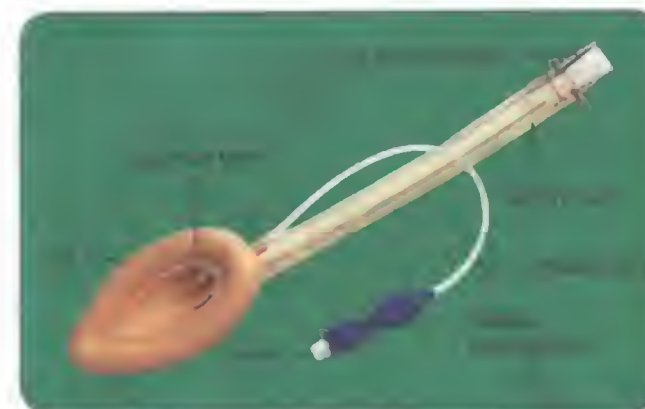


Fig. 29.7: Parts of the classic laryngeal mask airway
Source: LMA International



Fig. 29.8: Components of Fastrach laryngeal mask airway
Source: LMA International

END TIDAL CARBON DIOXIDE (ETCO₂)

- Alveolar gas is best represented by analyzing gas at end-expiration and therefore **ETCO₂ concentration at end expiration** is measured. This is **inversely proportional to alveolar ventilation**.
- **Brechner and Bethune** pioneered ETCO₂ monitoring.

Uses of ETCO₂

- ETCO₂ may be the first clue to the development of **malignant hyperpyrexia**.
- An indicator of the **degree and adequacy of alveolar ventilation**
 - To ensure **normocapnia** during mechanical ventilation
 - Control the level of **hypocapnia** in neurosurgery
 - Avoidance of **hypocapnia** where the cerebral circulation is impaired, e.g. the elderly.
- As a **disconnection indicator** if the reading subsequently falls to zero.
- To indicate **correct placement of endotracheal tube is in the trachea**.
- As an indicator of the **degree of rebreathing** (presence of carbon dioxide in inspired gas) e.g. using a Bain system.
- As an **indicator of cardiac output**.
- **Decreased ETCO₂** is seen in **air embolism**.

ETCO₂ during CPR

- Measurement of end tidal carbon dioxide (**ETCO₂**) during CPR reflects the **cardiac output** and **pulmonary blood flow** and **effectiveness of resuscitation**.
- During CPR
 - Gradual fall in ETCO₂ suggests compressionist fatigue >> time to change compressionists.
 - Abrupt rise in ETCO₂ suggests return of spontaneous circulation (ROSC) (detectable before pulse check).
- ETCO₂ at **20 minutes** of CPR is prognostically useful.
 - > 20 mm Hg at 20 minutes of CPR—higher chance of ROSC
 - < 10 mm Hg at 20 minutes of CPR—almost no chance of ROSC.

CAPNOGRAPHY

Capnometry is the measurement of CO₂ in gas mixture and capnography is the graphical recording of CO₂ concentration with time (capnogram). A normal capnogram has the phases as described here:

- **Phase I (inspiratory baseline)** begins at start of expiration and is normally zero, reflecting expired gases from respiratory dead space, which is normally devoid of carbon dioxide.
- **Phase II (expiratory upstroke)** is a rapid S shaped up-swing the transition between respiratory dead space (which does not participate in gas exchange), and alveolar gas from the respiratory bronchioles and alveoli.
- **Phase III is the plateau phase** because gas is coming entirely from the aveoli. The last portion of phase III is referred to as the end-tidal point. The CO_2 level here is normally at its maximum.
- An additional **phase IV (terminal upstroke)** before phase 0) may be seen in pregnancy.
- The angle between phases II and III is called **alpha angle** (normally 100–110 degrees).
- The angle between the end of phase III and descending limb of capnogram is called **beta angle** (normally 90 degrees).
- Thus, a normal capnogram has '3 phases' and '2 angles'.

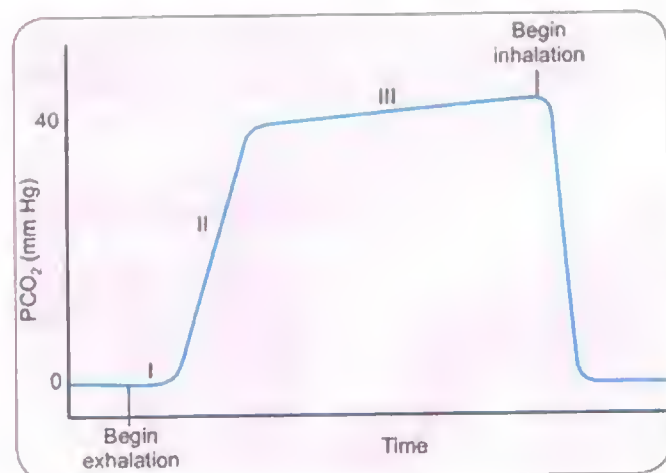


Fig. 29.9: A normal capnogram

Deviations from Normal Capnogram

- **Curare notch/Cleft (29.10):** Patient on controlled ventilation who is showing some spontaneous respiratory activities during respiratory cycle of controlled ventilation. It is usually present in the later third part of capnogram. It indicates that the **muscle relaxant is wearing off**.
- **Biphasic capnogram (29.11):** Has two peaks and is generally caused by
 - Unilateral hypoventilation

- Unilateral high airway pressure
- Single lung transplantation
- Endobronchial intubation or
- Severe kyphoscoliosis.
- **Capnogram not touching to baseline (29.12)** is normally caused by breathing of expired CO_2 and may be because of:
 - Exhausted CO_2 absorber (soda lime)
 - Malfunctioning expiratory valve
 - Extremely low flow of fresh gas.
- **Capnogram with increased alpha angle (29.13)** is normally caused by airway obstruction, either
 - Mechanical airway obstruction (tracheal tube kinking or blockade by secretions or foreign body)
 - Pathological airway obstruction (bronchial asthma, COPD).
- **Capnogram with increased beta angle (29.14)** may be caused by
 - Rebreathing during controlled ventilation with mapleson A
 - Malfunctioning inspiratory unidirectional valve in circle system.
- **Camel hump during inspiration** indicates rebreathing of mixed gas (alveolar and fresh) during later part of inspiration—typical of Mapleson D in controlled ventilation.

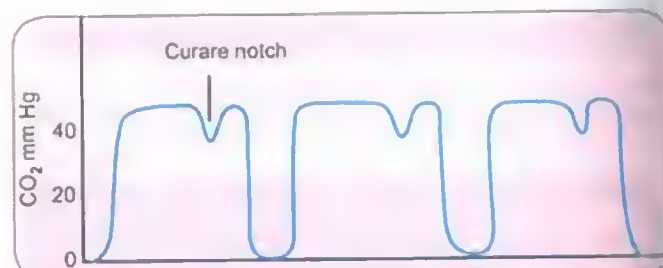


Fig. 29.10: Capnogram showing 'curare notch' indicating spontaneous respiratory efforts

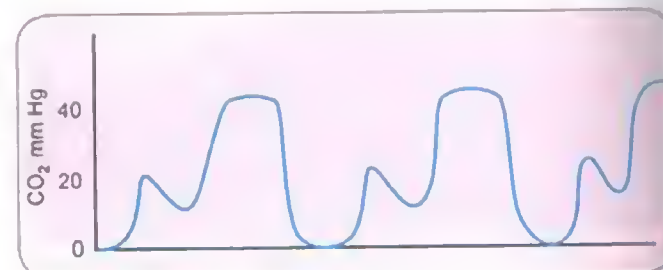


Fig. 29.11: Biphasic capnogram

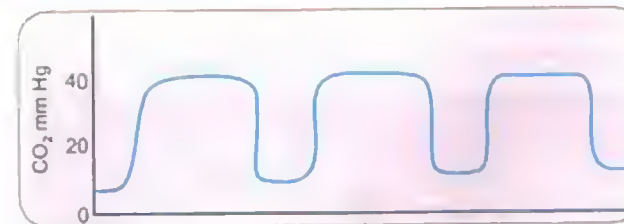


Fig. 29.12: Capnogram not touching the baseline



Fig. 29.13: Capnogram with increased alpha angle

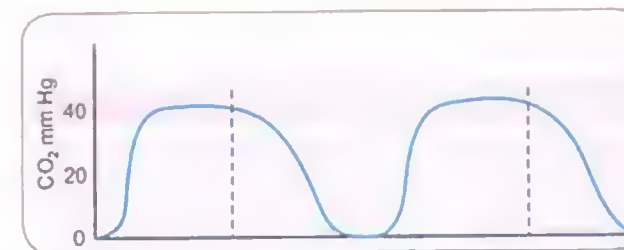


Fig. 29.14: Capnogram with increased beta angle

PULSE OXIMETRY

- Pulse oximetry is a simple noninvasive method of monitoring the **oxygen saturation of blood** (% of Hb saturated with oxygen).
- **Normal oxygen saturation** = 97–100%.
- Pulse oximetry is based upon **Beers-Lambert's law** which correlates concentration of solute (Hemoglobin) to intensity of light transmitted thro the solution. The typical pulse oximeter illuminates the tissue sample with two wavelengths of light: **660 nm red light** (which is well absorbed by deoxyhemoglobin, i.e. reduced Hb) and **940 nm infrared light** (which is well absorbed by oxyhemoglobin). By calculating the absorption at the two wavelengths the processor can compute the proportion of hemoglobin which is oxygenated.

Errors in Pulse Oximeter

- Carboxyhemoglobinemia
- Methemoglobinemia
- Intravascular dye (methylene blue)
- Low blood flow (hypovolemia)
- Nail polish
- Shivering and patient movement
- Ambient light

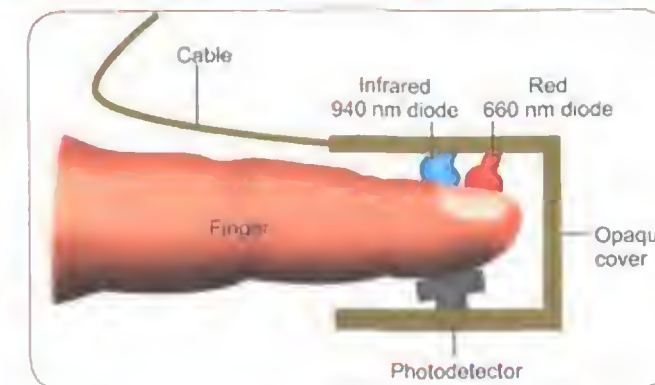


Fig. 29.15: Diagrammatic representation of a pulse oximeter probe

OXYGEN DELIVERY METHODS

- **First-line options**
 - **Standard nasal cannula:** Delivers an inspiratory oxygen fraction (FI_{O_2}) of 24–44%; flows ranging from 1–6 L/min. (NOTE: this also means that—'Maximum oxygen delivered by nasal cannula is 44%' at flow of 6L/min).
 - **Venturi mask:** It provides an accurate and constant FI_{O_2} —hence called 'fixed performance device'. Typical FI_{O_2} delivery settings are 24, 28, 31, 35 and 40% oxygen.
- **Second-line options**
 - **Simple face mask:** Delivers an FI_{O_2} of 40–60%; flows at 5–10 L/min. (NOTE: this also means that 'maximum oxygen delivered by simple face mask is 60%'.
 - **Non-rebreathing face mask with reservoir and one-way valve:** It may deliver FI_{O_2} up to 90%; 8–10 L/min.
 - **Reservoir cannulas;** flows of 8 L/min.
 - **High-flow transtracheal catheters**
 - **High-flow warmed and humidified nasal oxygen:** Nasal oxygen has been administered at flows ranging from 10–40 L/min.
- Room air provides **21% oxygen**.

Oxygen Toxicity

Oxygen has side effects in overdose—during routine administration of oxygen in hospitals or during hyperbaric oxygen therapy. They are:

- **Vasoconstriction:** Coronary, cerebral and renal vasculature—could lead to hypoperfusion.
- **CNS toxicity:** Confusion, seizures - **Paul Bert effect**.
- **Retinopathy of prematurity (ROP)**
- **Bronchopulmonary dysplasia (BPD)**
- **Acute tracheobronchitis**

- Lung toxicity includes:
 - Interstitial **edema** and **fibrosis** (Lorraine Smith effect)
 - Ventilation Perfusion **mismatch**
 - **Haldane** effect (acidemia)
 - Absorption **atelectasis**
 - **Increased** work of breathing
 - **Decrease** in lung volumes and compliance.
 - ARDS
 - Pulmonary vasodilation.

CENTRAL VENOUS PRESSURE (CVP)

Procedure

- **MC used** and **Ideal vein** is **right IJV** since it is **short, straight and valveless** ('Right is always right!').
- Advantages of right IJV are accessible from head end of table; predictable anatomy and high success rate.
- Other veins that can be cannulated are **subclavian** (**pneumothorax MC**), **femoral** and **antecubital**.
- Introduced by **Seldinger** technique.
- **The tip of the catheter** should be at the junction of SVC and right atrium.
- The **CVP** parallels the **right atrial pressure**.
- **Normal CVP** is **5–10 cm H₂O**; **2–7 mm Hg**.

Indications for CVP Measurement

- Total parenteral nutrition
- Open heart surgeries
- Fluid management in shock
- Aspirating air embolus
- Major surgeries where fluctuation in hemodynamics is expected.

Increased CVP	Decreased CVP
<ul style="list-style-type: none"> • Fluid overload • RV failure • Pulmonary embolism • Cardiac tamponade • Constrictive pericarditis • Hemothorax 	<ul style="list-style-type: none"> • Hypovolemia and shock • Venodilation

STAGES OF ANESTHESIA

The stages are seen with **Ether anesthesia** and were described by **Guedel**.

- **Stage I:** Stage of **analgesia**: From beginning of anesthesia to loss of consciousness. Because **hearing is the last sense to be lost**, the conversation of operating room staff should be guarded during this stage
- **Stage II:** Stage of **delirium**: From loss of consciousness to onset of automatic breathing.
- **Stage III:** Stage of **surgical anesthesia**: From onset of automatic breathing to respiratory paralysis; entire relaxation, no muscular rigidity and deep regular breathing.

- **Stage IV:** Stage of **respiratory (medullary) paralysis** from stoppage of respiration till death.



Fig. 29.16: Sensor applied to forehead (note the position of the electrodes)—Bispectral index

MONITORING DEPTH OF ANESTHESIA

- **Bispectral index:** **MC used method**; electrode strip is placed over the patients forehead and electrical activity is recorded in form of **EEG** – this is analyzed by the **BIS** machine and a number is generated; **when patient is awake, cerebrocortical activity is more and a higher number is generated.**
 - 100–85: **Awake** and capable of explicit recall.
 - 85–60: **Increased sedation**, impaired memory processing but rousable with stimulation.
 - 60–40: **Surgical anesthesia.**
 - 40–0: **Burst suppression**, electrical silence.
- Other methods used for **monitoring depth of general anesthesia** are: **Raw EEG**, **power spectral analysis**, **auditory evoked potentials**, **Tinnsall's isolated forearm technique**, **lower esophageal contractility**.

PREOPERATIVE RISK ASSESSMENT

ASA Physical Scale

American Society of Anesthesiologists (ASA) scale is used for **preoperative risk assessment** as here.

Class	Physical status
1	Healthy patient with NO disease process.
2	Patient with mild to moderate systemic disease NOT limiting functional activity, e.g. treated hypertensive , stable diabetics . Patients aged ≥ 80 years are automatically placed in class 2.

Contd...

Contd...

Class	Physical status
3	Patient with severe systemic disease that LIMITS functional activity, e.g. ischemic heart disease, COPD.
4	Patient with severe systemic disease which is constant threat to life , e.g. Unstable angina.
5	Moribund patient unlikely to survive 24 hours with or without surgery.

Cardiac Risk Factors for Noncardiac Surgery

Major risk factors	<ul style="list-style-type: none"> • Recent acute Ischemic MI (within 1 month) • Unstable angina • Decompensated CHF • Severe valvular disease • Arrhythmias (including high grade AV block, symptomatic ventricular arrhythmia) with uncontrolled ventricular rate.
Intermediate risk factors	<ul style="list-style-type: none"> • Angina • Previous MI (> 1 month prior to planned surgery) • Compensated CHF • Diabetes mellitus • Renal insufficiency (creatinine > 2mg/dL)
Minor risk factors	<ul style="list-style-type: none"> • Advanced age • Non-sinus rhythm • Hypertension • H/O stroke

NYHA Classification

Class I	NO limitation of physical activity Ordinary physical activity does NOT cause undue fatigue, dyspnea, or anginal pain
Class II	SLIGHT limitation of physical activity Ordinary physical activity results in symptoms
Class III	MARKED limitation of physical activity Comfortable at rest, but less than ordinary activity causes symptoms
Class IV	UNABLE to engage in any physical activity without discomfort Symptoms may be present even at rest

Revised Cardiac Risk Index (RCRI)

- Estimates risk of cardiac complications after surgery
- H/O ischemic heart disease
- H/O congenital heart disease
- H/O cerebrovascular disease (stroke or TIA)
- H/O diabetes requiring preoperative insulin use
- Chronic kidney disease (creatinine > 2 mg/dL)
- High risk surgery—Undergoing suprainguinal, vascular, intraperitoneal or intrathoracic surgery

EXTRA EDGE

In above **RCRI**:

- 0 points = 0.4% risk of major cardiac event
- 1 point - 0.9%
- 2 points - 6.6%
- ≥ 3 points - $> 11\%$

EEG PATTERNS DUE TO ANESTHESIA

- **EEG slowing** during induction of anesthesia is due to **hypothermia**.
- At Sub MAC concentrations (lighter levels of anesthesia)—EEG shows **WAR** (widespread anterior maximum rhythmic activity) similar to beta-alpha frequency range (8–15 Hz); this stage may also show **WPW** (Widespread persistent Delta Waves).
- Supra-MAC anesthetic concentrations. Large doses of anesthetics **shift the EEG from theta to delta**, with **increased slowing** and finally a decrease in amplitude with **burst-suppression** and ultimately total loss of EEG activity.

DRUGS TO BE MODIFIED PREOPERATIVELY

Continue on day of surgery	Discontinue on day of surgery
<ul style="list-style-type: none"> • Antidepressant, anti-anxiety and psychiatric medications (including MAO inhibitors) • Antihypertensives (ACE inhibitors and ARB-Angiotensin receptor blockers can be stopped 12–24 hours before if taken only for hypertension) • Birth control pills • Asthma medications • Cardiac medications • COX-2 inhibitors • Eyedrops • Diuretics (triamterene, hydrochlorothiazide) • Statins • Thyroid medications • Antiepileptics • Steroids (oral or inhaled) • Methotrexate (If no risk of renal failure) • Insulin (with doses modification) 	<ul style="list-style-type: none"> • Oral hypoglycemic agents • Viagra (stop before 24 hours) • Warfarin (stop 5 days before) • Potent loop diuretics • Vitamins, minerals and iron • Herbal supplements • Topical creams

Aspirin and Surgery

Traditionally aspirin was stopped before surgery; BUT now it is under scrutiny.

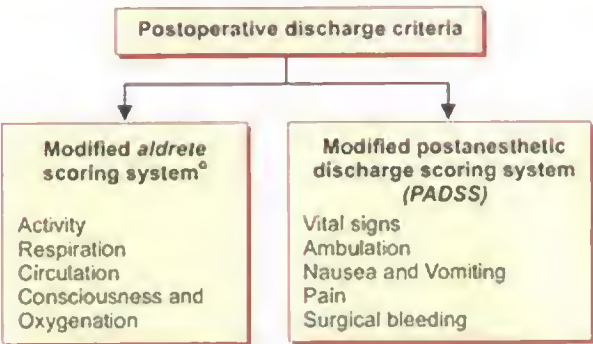
Continue aspirin on day of surgery in	Discontinue 5–7 days before surgery
<ul style="list-style-type: none">• Patients with known vascular disease• Patients with drug eluting stents < 12 months• Patients with metal stents for < 1 month• Before cataract surgery (if no bulbar block)• Before vascular surgery• Taken for secondary prophylaxis	<ul style="list-style-type: none">• If risk of bleeding > risk of thrombosis• For surgeries with serious consequences from bleeding• Taken only for primary prophylaxis (non known vascular disease)

Clopidogrel and Surgery

Continue clopidogrel on day of surgery	Discontinue 5–7 days before surgery
<ul style="list-style-type: none">• Patients with drug eluting stents < 12 months• Patients with metal stents for < 1 month• Before cataract surgery (if no bulbar block)	<ul style="list-style-type: none">• Patients not included in the group recommended for continuation• Stop 7 days before spinal/epidural blockade

POSTOPERATIVE DISCHARGE CRITERIA

- Criteria for discharge of patients from postanesthetic care unit.
- The original Aldrete score had visual observation of 'color' as a measure of oxygen saturation—BUT this has been replaced by pulse oximetry now in modified Aldrete; similarly the PADSS had originally fluid intake/output as a criteria which was later removed in modified PADSS.



AIR EMBOLISM DURING ANESTHESIA

- Venous air embolism is MC in sitting cariotomies.

- **Diagnosis of air embolism:**
 - Sudden *decrease* in $ETCO_2$
 - Sudden *increase* in ETN_2 (End tidal nitrogen)
 - Sudden *attempts to self ventilate* by patients who are being mechanically ventilated.
- **Best method to confirm diagnosis** is transesophageal echocardiography (TEE); next best method is *precordial Doppler U/S* (but this is the best NON-invasive method).
- TEE is *invasive, expensive, most sensitive*, MUST be *continuously monitored* can detect as low as *0.02 ml/kg of air* (BUT it is NOT quantitative) and may *interfere with Doppler* monitoring.
- **Treatment:** Flood surgical field with saline; deliver 100% oxygen; aspirate central venous catheter; give volume to increase CVP; treat hemodynamic changes appropriately.

MEDICAL GAS SUPPLY

- **Boyle's apparatus:** Anesthetic machine.
- Anesthetic gas cylinders are made of **chromium molybdenum steel**.
- Cylinders are named from *small to large size* as B, C, D, E, F, AF, G, J.



Fig. 29.17: Boyle's apparatus

- Size E weighs 5.4 kg and is commonly used on the anesthetic machine.
- A small **metal and neoprene seal (Bodok seal)** ensures a gas tight fit between the cylinder and anesthetic machine yoke.
- The **pressure in anesthetic gas pipelines is 4 bar (or 50 psi)**—the same as the working pressure of the anesthetic machine.

Color of Medical Gas Cylinders

Oxygen	Nitrous oxide	Entonox	Carbon dioxide	Cyclopropane	Ethylene	Halothane	Helium
Black with white shoulder	Blue	Blue with white /blue quartered shoulders	Grey	Orange	Red	Amber bottle	Brown
							

- An **vaporizer** is a device generally attached to an anesthetic machine which delivers a given concentration of a volatile anesthetic agent. A vaporizer converts the liquid inhalational agent into a gas form that can be delivered by the inhalational route to the patient. **Desflurane** has a *very low boiling point* and hence requires a *special heated vaporizer* (heated to 39°C). **Vaporizers** are made of metals with *high thermal conductivity* (**copper, bronze**) to further *minimize heat loss*.
- The colors of cylinders are given here, but they differ in some countries like USA.

Pin Index

In order to ensure that the correct cylinder is attached to the yoke of the anesthetic machine a series of pins on the machine yoke is made to fit an identical pattern of indentations on the cylinder. This is called the **Pin-Index safety system (PISS)**.

Oxygen	2 and 5
Nitrous oxide	3 and 5
Entonox	7
Carbon dioxide	1 and 6
Cyclopropane	3 and 6
Air	1 and 5

Diameter Index Safety System

Non-Interchangeable Screw Thread (NIST) or Diameter Index Safety System (DISS): Used for pipeline gases, which prevents piped gases from the well being accidentally connected to the wrong inlet on the machine!.

Cylinder Pressures

Oxygen	137 bar, 2200 psi
N ₂ O	40 bar (liquid), 760 psi
CO ₂	50 bar (liquid)
Cyclopropane	5 bar (liquid)

Cylinder pressure is usually measured by a **Bourdon pressure gauge**.

ANESTHESIA MACHINE

The anesthesia machine is divided into three parts:

1. The **high pressure system** consists of all parts of the machine which **receive gas at cylinder pressure**, reduces the pressure and makes it more constant. These include the following:
 - The **hanger yoke** which connects a cylinder to the machine
 - The **yoke block** used to connect cylinders larger than size E or pipeline hoses to the machine through the yoke
 - The **cylinder pressure gauge (Bourdon's gauge)**, which indicates the gas pressure in the cylinder
 - The **pressure regulator**, which converts a high variable gas pressure into a lower, more constant pressure, suitable for use in the machine.
2. The **intermediate pressure system** which receives **gases at reduced pressure**. The parts of the intermediate pressure system are:
 - **Pipeline inlet connections** which connect the machine to the hospital pipeline system
 - **Pipeline pressure gauges**
 - **Ventilator power outlets** which supplies driving gas to the ventilator

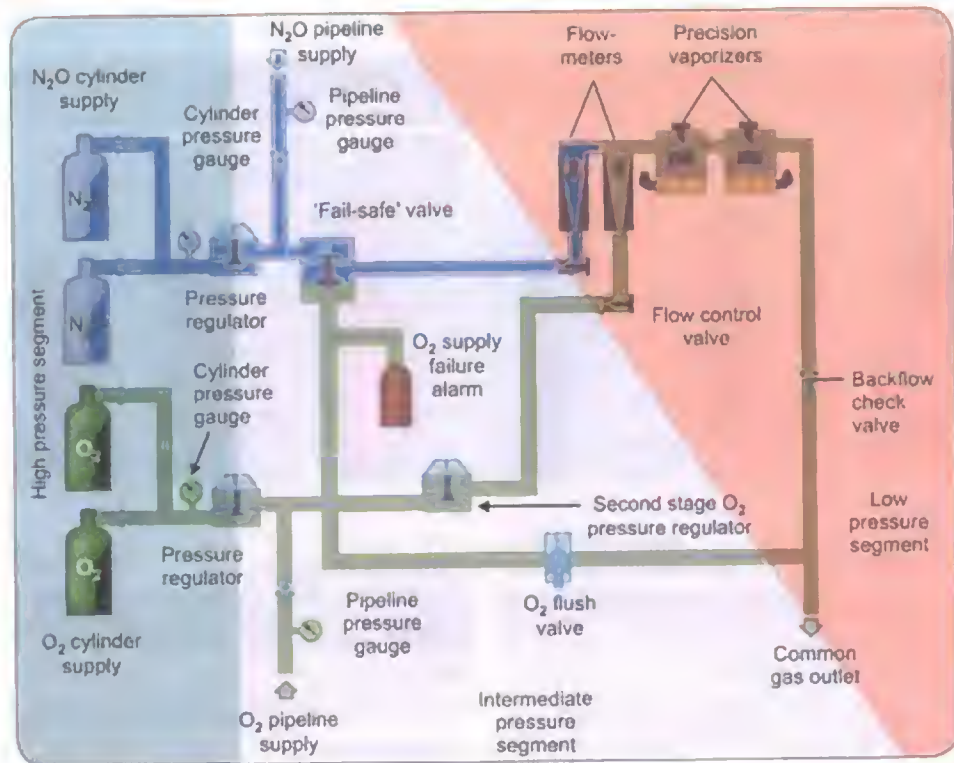
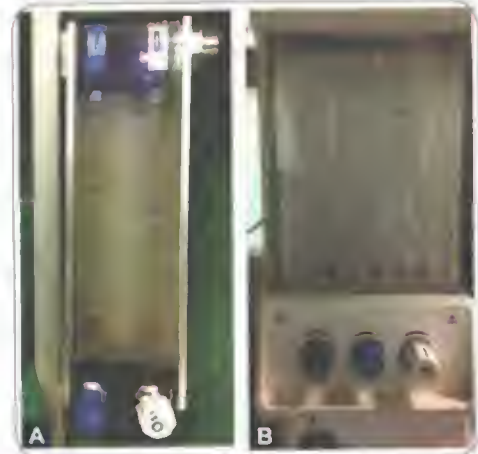


Fig. 29.18: Schematic diagram of continuous flow anesthesia machine

- **Oxygen pressure failure devices** which either interrupt the flow of anesthetic gases or provide an alarm when the oxygen supply fails
 - **Second stage pressure regulators**
 - **Oxygen flush** which allows delivery of high flow of oxygen from the machine
 - **Flow control valves**
 - **Auxiliary oxygen flow meters.**
3. The **low pressure system** takes the gases from the flowmeters to the machine outlet. It is the part of the machine downstream of the flow meters in which the pressure is slightly above the atmospheric. This includes:
- Flowmeters
 - Antihypoxia devices
 - Vaporizers mounted on the back bar
 - Vaporizer circuit control valves
 - Back flow check valve and
 - The common gas outlet.

Flowmeters

- Flowmeters (**Thorpe tubes**) are made up of pyrex glass and bobbin is made of aluminium.
- In modern anesthesia machines, **oxygen flowmeter is always positioned downstream** (or last or right extreme) in a sequence of flowmeters, so that if there is any leakage anywhere upstream of any other gas, still oxygen will be delivered in a sufficient concentration (if oxygen flowmeter is upstream a hypoxic mixture will be delivered to the patient!).



Figs 29.19A and B: Different types of flowmeters (rotameters) on anesthesia machines

ANESTHETIC BREATHING SYSTEMS/ANESTHETIC CIRCUITS

- In spontaneously breathing patients, gases travel from the anesthetic machine via an '**Anesthetic circuit**' (more correctly an **Anesthetic breathing system**).
- Contact with patient is made via facemask, laryngeal mask or tracheal tube. There are **5 basic systems** referred to as '**Mapleson A, B, C, D, E**'.

- All breathing systems consist of the following:
 - A connection for fresh gas input
 - A reservoir bag: usually of 2-liter capacity to allow the patients peak inspiratory demands (30–40 l/min) to be met with a lower constant flow from the anesthetic machine.
 - An adjustable expiratory valve.
- Mapleson analyzed and described 5 different arrangements of fresh gas inflow tubing, reservoir tubing, facemask, reservoir bag and an expiratory valve to administer anesthetic gases. These 5 **semi-open anesthetic systems** are designated Mapleson A to E.
- Fresh gas inlet is **nearer to patient in D, E, F**.
- **Valveless circuits** are E and F.

Mapleson Circuits

- **Mapleson A (Magill system):** circuit of choice for **Spontaneous ventilation in adult**. ('SPAM')
- **Mapleson C (Water system), 'C = Sea water!'**
- **Mapleson E system** or Ayre's T piece
- **Mapleson F (Jackson Rees modification of Mapleson D):** Circuit of choice for **children**.
- **Bain circuit:** **Cooxial** version of **Mapleson D** system—Circuit of choice for **controlled ventilation in adult** ('BCD').

- Fresh Gas Inflow Rate**
- HIGH in Mapleson systems
 - Moderate in semiclosed circle systems
 - Low in closed circle systems

- Mapleson Systems Ranked in Order of Efficiency**
- Controlled ventilation: **D > B > C > A** (**Dead Bodies Can not Argue!**)
 - Spontaneous breathing/ventilation: **A > D > C > B** (**All Dogs Can Bite!**).

- Circle Systems**
- An alternative to using high flow circuits is to absorb CO₂ from the expired gases, which are then **recirculated** to the patient; these circuits are known as **circle systems**.
 - **CO₂ is removed** from the expired gas by passage through **soda lime, baralyme or Amsorb plus**.
 - Additional advantages of using circle systems in that the gases within the circle are warmed and humidified prior to inspiration.
 - **Drugs contraindicated in circle systems:** **Trichloroethylene, Sevoflurane, Methoxyflurane and Chloroform**. ('**TRY SAVING ME from Chloroform!**').

CO₂ ABSORBENTS

- Soda Lime**
- **MC used CO₂ absorbent.**
 - Soda lime **granules** consist of **water, 94% calcium hydroxide (most important)** and **5% sodium hydroxide, and 1% potassium hydroxide**, which reacts with CO₂ to form **calcium carbonate**.
 - **Silica** is added to granules to **provide hardness and prevent alkaline dust formation**.
 - As more CO₂ is absorbed the pH decreases and the color of the dye changes from **pink to yellow/white** (**Clayton yellow - pH indicator**).

- Baralyme**
- **Baralyme** (barium hydroxide lime) contains **5% barium hydroxide (instead of sodium hydroxide), 80% calcium hydroxide and 6% potassium hydroxide**.
 - It is said to be less caustic and to produce less heat than soda lime.
 - **NO silica** is necessary to produce hardness.
 - It contains **Mimiza Z** and **ethyl red as indicator**; the pink granules change to purple when exhausted.

- Amsorb Plus**
- Contains **calcium hydroxide, calcium chloride and water**.
 - Hardness is provided by **calcium sulfate and polyvinyl pyrrolidone**.

XENON ANESTHESIA

Advantages	Disadvantages
<ul style="list-style-type: none">• Inert has no metabolism• Nontoxic• Nonexplosive• Very low blood gas partition (solubility) coefficient (0.14-0.20)• Very rapid induction and recovery• Minimal CVS effects• Does not trigger malignant hyperthermia• Environment friendly	<ul style="list-style-type: none">• Very high cost• Low potency (MAC = 71)• No commercially available anesthetic equipment using xenon

FEW PROCEDURES

- Cricoid Pressure (Sellick's Maneuver)**
- The cricoid cartilage is the only **complete** ring of cartilage in the larynx.

- Pressure exerted upon it anteroposteriorly forces the whole ring posteriorly, compressing the esophagus against the body of the sixth cervical vertebra, thereby **preventing passive regurgitation**.

Heimlich Maneuver

- Used as **emergency first aid for relief of choking (foreign body obstructing airway)**.
- This aims to produce a **rapid rise in intrathoracic pressure** by forcing the diaphragm into the chest, and expel the foreign body.

SPINAL ANESTHESIA

- **Site:** L3-L4 space in **adults**; L4-L5 space in **children**.
- **Tuffier's line:** It is a horizontal line drawn between the superior borders of the iliac crests and corresponds to either L4 vertebral body or L4-L5 interspace.

Structures that the needle will pierce

- Skin/Subcutaneous fat, fascia
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Epidural space
- Dura mater
- Arachnoid mater
- Subarachnoid space – CSF
- Thus, the drug is deposited **between arachnoid and pia mater**.

EXTRA EDGE

- When performing lumbar puncture, a '**snap/pop**' is felt just before entering the epidural space when the needle pierces the **ligamentum flavum**.

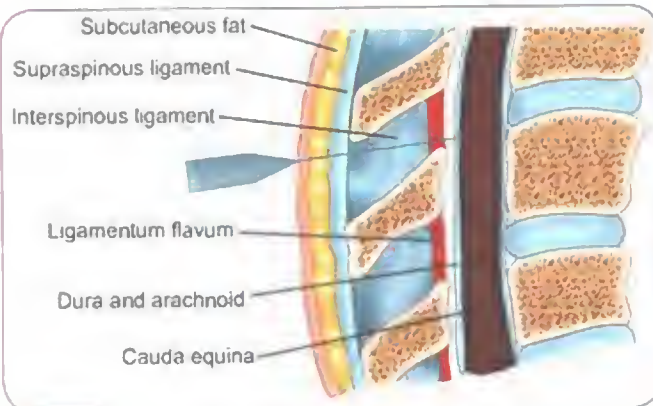


Fig. 29.20: Structures that the needle will pierce



Fig. 29.21: Quincke's needle

Order of Blockade

- **Quincke-Babcock needle** is the **MC** used needle for lumbar puncture during spinal anesthesia.
- The thinnest/finest nerves get blocked first by local anesthetics.
- **First fibers affected** are autonomic—**preganglionic sympathetic (small C fibers) > temperature (cold before warmth) > pinprick > pain > touch > pressure > motor > vibration > proprioception**.
- **Recovery—It is in reverse order; BUT preganglionic sympathetic recovers first.**

Baricity

- Local anesthetic agents are either **heavier (hyperbaric)**, **lighter (hypobaric)**, or have the same specific gravity (**isobaric**) as the CSF.
- Hyperbaric solutions tend to spread below the level of the injection, while isobaric solutions are not influenced in this way.
- It is **easier to predict** the spread of spinal anesthesia when using a hyperbaric agent.

Drugs

- **Bupivacaine:** 0.5% **hyperbaric** (heavy) **is the best agent to use**; it lasts longer than most other spinal anesthetics; usually 2-3 hours.
- **Lignocaine:** 5% hyperbaric (heavy) lignocaine gives best results, which lasts 45-90 minutes. If 0.2 ml of adrenaline 1:1000 is added to the lignocaine, it will **usefully prolong its duration of action**. Lignocaine from multi-dose vials should **NOT** be used for intrathecal injection as it contains potentially harmful preservatives.

Factors Affecting Height or Level of Block

- Volume of drug—**more volume, more the height of block**
- Height of patient—In **tall patients more drug is required**

- **Pregnancy:** In pregnancy, **lower dose of drug** is required due to **decreased volume of subarachnoid space, engorged epidural veins** and **increased sensitivity to local anesthetic drugs**.

Complications of Spinal Anesthesia

- Hypotension (MC complication)
 - **Prophylactic Rx:**
 - **IV fluids:** Traditionally **preloading** (giving IV before inducing spinal anesthesia) with 1.5 L of RL solution (crystalloid) was used; BUT recent evidence suggests **colloid** (hydroxyethyl starch, HES) is **more effective**. ALSO **co-loading** (i.e. giving fluid as the block is establishing) is **more effective** than preloading.
 - **Vasopressor agents:** **Phenylephrine** is better than **ephedrine** (since ephedrine has more chances of fetal acidosis).
- Postspinal headache
 - Due to **CSF leaking** from a **dural puncture**.
 - Usually **occipital**, relieved on lying down, lasting for 7-10 days.
 - Prevention:
 - Use **small bore needle**.
 - Use **atraumatic needle** (Whitaker or Sprotte needle with pencil point tip—splits dural fibers) rather than **Quincke-Babcock needle** (beveled tip, dura cutting needle).
 - **Adequate hydration**.
 - Avoid sitting position postoperatively.
 - Curative: Lie supine, analgesia, abdominal binder, epidural blood patch.

Total Spinal Anesthesia (High block)

- Sensory block that rises **above the cervical region**; it is unintentional and may occur due to patient movement, inappropriate positioning or inappropriate dose of local anesthetic.
- Manifests as **bradycardia, hypotension, dyspnea, inability to speak and cough, difficulty in swallowing and loss of consciousness**.
- Treat supportively with oxygenation, ventilation and maintain circulation with intravenous fluids and vasopressors such as ephedrine until the block wears off (usually wears off rapidly)

CAUDAL EPIDURAL ANESTHESIA

- Anesthesia and analgesia below the umbilicus
 - For **superficial operations** such as skin grafting, perineal procedures, and lower limb surgery. A

general anesthetic will often be required in addition. **Pain relief** will extend into the postoperative period.

➤ The **duration of the block can be prolonged** by the addition of an opiate (pethidine) to the local anesthetic.

- Obstetric analgesia (neuraxial analgesia)
 - **Analgesia of choice** for **1st stage (T10-L1 block)** and **2nd stage (T10-S4 block)** of labor; for **instrumental deliveries** and also for delivery in valvular heart disease (**mitral stenosis**) patients.
- Analgesia for chronic pain
 - For pain such as **leg pain after prolapsed intervertebral disc, or post shingles pain** below the umbilicus.

Methods to locate epidural space

- Negative pressure test
- Hanging drop method
- Loss of resistance
- Macintosh extradural space indicator.

Complications

- **Headache**
- **Intravascular or intraosseous injection:** This may lead to grand mal seizures and/or cardiorespiratory arrest.
- **Dural puncture:** Extreme care must be taken to avoid this, as a **total spinal block will occur if the dose for a epidural block is injected into the subarachnoid space**. The incidence of **dural puncture in experienced hands should be less than 1%** for epidural anesthesia. See under 'complications of spinal anesthesia' above, for more about total spinal block.
- **Perforation of the rectum:** While simple needle puncture is not important, contamination of the needle is extremely dangerous if it is then inserted into the epidural space.
- **Sepsis:** This should be a very rare occurrence if strict aseptic procedures are followed.
- **Urinary retention:** This is not uncommon and temporary catheterization may be required.
- **Subcutaneous injection.** This should be obvious as the drug is injected.
- **Epidural hematoma, bloody tap**
- Absent or **patchy block/missed segments**—In **epidural anesthesia, missed segments or unilateral block** may occur in over 2% of patients.
- The possibility of **delayed respiratory depression** from epidural opiates needs taken into account, and patients should monitored in an intensive care or

high dependency unit for 24 hours following their administration.

- **Remifentanyl** is **contraindicated** for epidural analgesia.
- **Hypotension** (The **hypotension** produced by **epidural anesthesia** being **slower in onset** than in spinal anesthesia **can often be compensated for by fluids alone**, but in both cases, a small dose of a vasopressor agent may be needed.)



Figs 29.22A to C: Tuohy needle with its curved tip magnified

Comparison of Some Aspects of Spinal and Epidural Anesthesia

Feature	Spinal anesthesia	Epidural anesthesia
Time to onset	Fast	Slower
Reliability of block	Very high if good flow of CSF	Not as high
Patchy block	Very rare	Can occur because of incomplete spread
Distribution of block	Effectively transects the neural input at the level of block	Can produce a band of anesthesia over several dermatomes leaving lower ones free
Modality affected	Affects all motor and sensory functions	Dose of some drugs will partially spare motor functions
Ability to adjust level of block	After the dose is in, only baricity and positioning are available for adjustment	Easy to achieve if catheter is in position
Test dose	Not required	Recommended by many practitioners
Systemic toxicity	Much lower doses, so less dangerous	Large volumes of local anesthetics

Contraindications for Neuraxial (Spinal and Epidural) Anesthesia

- Patient refusal
- Infection at needle insertion site
- Hypovolemic shock
- Increased ICT from mass lesion
- Significant coagulopathy (platelets < 50,000)
- Stop ticlopidine 14 days before and clopidogrel 7 days before neuraxial block.

INTRAVENOUS REGIONAL ANESTHESIA (IVRA, BIER'S BLOCK)

- IVRA is a simple method of producing anesthesia **in arm/leg**; it involves IV injection of large volumes of dilute local anesthetic into an extremity after **occlusion of circulation by a tourniquet**.
- IVRA is **indicated** for any procedure on the **arm below the elbow**, or **leg below the knee**, that will be completed **within 2 hours**.
- Contraindications: **If a tourniquet cannot safely be used** (e.g. In patients with severe Raynaud's or homozygous sickle cell disease).
- The **only equipment** necessary to perform this procedure successfully is a **tourniquet which does not leak** and that **can be inflated to a pressure at least 100 mm Hg above the patient's systolic blood pressure**, and a cannula inserted in a distal vein.
- **Drug of choice** for IVRA is **preservative free prilocalne without adrenaline**.
- If prilocalne is not available, **lignocaine** is acceptable.
- **Bupivacaine** is **contraindicated**—causes refractory cardiac dysrhythmias and arrest.

CELIAC PLEXUS BLOCK

- The **MC use of neurolytic celiac plexus block** is to treat **pain a/w intra-abdominal malignancy in upper abdomen**; particularly pain a/w **pancreatic cancer**.
- The celiac plexus lies at T12-L1 level; block is performed both on the right and left side.
- **Physiologic effects** following celiac plexus block include: **Orthostatic hypotension; sudden diarrhea and abdominal cramping, hiccups**.
- **Complications** include: **Retroperitoneal hematoma, abdominal aortic dissection, paraplegia, interscapular back pain, reactive pleurisy, hematuria, pneumothorax**.

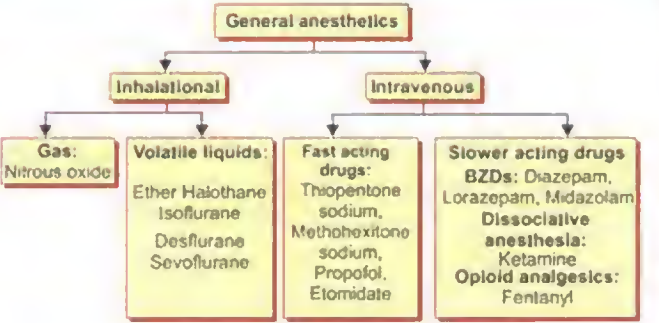
STELLATE GANGLION BLOCK

- Stellate ganglion is formed by the fusion of the **lower cervical and first thoracic** ganglion. It is blocked anterior to the tubercle of transverse process of C7 vertebra, i.e. **chassaignac tubercle** at the level of cricoid cartilage.
- **Signs of successful block** are: **Horner syndrome** (ptosis, miosis, enophthalmos, anhidrosis, absence of ciliospinal reflex); **flushing of face, conjunctival congestion**, nasal stuffiness (**Gutman's sign**); injection of tympanic membrane (**Muller's syndrome**), increased **skin temperature** and **lacrimation**.
- Indicated in: Treating acute herpes zoster in the face, upper thorax; reflex sympathetic dystrophy syndrome, frostbite, Raynaud's syndrome of upper limbs.

BRACHIAL PLEXUS BLOCK

- **Brachial plexus block** is used for upper limb surgeries between the shoulder and fingers.
- Usually performed with ultrasound guidance these days.
- Approaches used are:
 - **Supraclavicular approach** (MC used)
 - Ventral infraclavicular
 - Axillary
 - Interscalene

GENERAL ANESTHETICS



Agents no longer used

- Cyclopropane
- Methoxyflurane (Fluoride ion nephrotoxicity); most potent anesthetic, lowest MAC
- Trichloroethylene [arrhythmogenic; never use trichloroethylene in a circle with soda lime as the toxic compounds phosgene (pulmonary irritant) and dichloroacetylene (cranial neurotoxin) are produced]; most potent analgesic
- Enflurane (Epileptogenic)

INTRAVENOUS ANESTHETIC (INDUCTION) AGENTS

Sodium Thiopentone

- Pharmacology**
- **Ultra-short acting barbiturate**; induction of anesthesia is **rapid and smooth**; **poor analgesic**.
 - Patient may complain of **tasting onions or garlic** during administration.
 - Consciousness usually returns after 4–10 minutes as a result of **redistribution**.
 - It is presented as a **pale yellow powder**; the vial contains **sodium carbonate and nitrogen** in place of air. These two measures are designed to **improve the solubility** of the solution.
 - Sodium carbonate reacts with water forming sodium bicarbonate resulting in a **strongly alkaline solution (pH 10.5 to 11)**; **2.5% solution** is stable for many days.
 - **Thiopentone is contraindicated** in porphyria, status asthmaticus, severe shock, pericardial tamponade, uncompensated myocardial disease.
 - **DO NOT** prepare with ringer lactate since it will **precipitate due to acidic pH of ringer lactate**.

Systemic Effects

- **Hypotension** may occur secondary to **myocardial depression and venodilatation**.
- Potent **anticonvulsant**, **↓ cerebral metabolism**, **↓ cerebral blood flow** and **↓ intracranial tension (ICT)** - hence safe in **traumatic brain injury (DOC in head injury)** patients; also **↓ intraocular pressure (IOP)**.
- May **exacerbate porphyria**.
- It shunts blood from non-ischemic to ischemic areas of brain so it protects brain from focal ischemia (but not from global ischemia). This phenomenon is called 'reverse steal phenomena' or '**Robin Hood effect**'.

Accidental Intra-arterial thiopentone injection

- This causes **immediate pain and blanching**; **arterial obstruction** is due to **vascular spasm and obstruction by thiopentone crystals**.
- Treatment**
 - Leave needle in place; Irrigate with **saline**.
 - Start **anticoagulation** with heparin and then warfarin for 2 weeks.
 - Give 10 mL of **1% procaine** to buffer thiopentone and act as local anesthetic.
 - Consider **papaverine** 40 mg, **phenoxybenzamine** 0.5 mg or urokinase.
 - Sympathetic block, e.g. **brachial plexus block**.
 - Keep limb warm and elevated and continue with GA to dilate vessels.

EXTRA EDGE

- **Methahexitane:** Shorter acting barbiturate than thiopentone.

Propofol (Diisopropylphenol)

- **MC used IV induction and maintenance agent.** Suitable for **day care surgery**; in **ICU** and for **interventional radiology** procedures.
- It is prepared as an **emulsion in soya bean oil and egg phosphatide**; **pain/burning during injection can occur**; very **highly protein bound (98%)**.
- **NOT approved** for long-term sedation in children.
- Propofol is **safe** for patients with **acute intermittent porphyria**; does **NOT** trigger malignant hyperthermia; **intra-arterial injection causes less nausea and vomiting (has anti-emetic effect)**.
- Side effects:
 - **Apnea**; **metabolic acidosis**, **lipemia**, **heart failure**; pain at injection site
 - **Propofol infusion syndrome** (acute refractory bradycardia, asystole, metabolic acidosis, rhabdomyolysis, hyperlipidemia, fatty liver) when propofol infused for more than 48 h at 4 mg/kg/hr.
- **Fospropofol:** A **water soluble prodrug of propofol** approved for **sedation and monitored anesthetic care (MAC)**.

Etomidate

- Used in **rapid sequence induction**; has very **minimal cardiovascular effects (cardiostable)**.
- **Prolonged use suppresses adrenocortical function**, impairing recovery in critically ill patients.
- Etomidate also **activates seizure foci** and is **contraindicated** in patients with **epilepsy**.
- Etomidate is highly **Emetic**.

Ketamine

Pharmacology

- A **phencyclidine derivative**; an **NMDA receptor antagonist**.
- Causes '**dissociative anesthesia**' which implies that the patient is detached from their surroundings; **vivid hallucinations** are common during recovery (**emergence delirium**) and can be minimized by concurrent use of **benzodiazepines** (e.g. midazolam).

Systemic Effects

- ↑ **BP**, ↑ **IOP**, ↑ **ICT**; (also increases cerebral metabolic rate and cerebral blood flow); may be **dangerous for hypertensives** and in **IHD**; **AVOID** in **epileptics**.

Contd...

Systemic Effects

- However **heart rate, BP, cardiac output** are **well-maintained** even in **shocked patients**—so it is **useful in emergency surgery (hypovolemic patients)**.
- **Laryngeal reflexes** are better maintained and **bronchodilatation** occurs—preferred in **asthmatics** and **status asthmaticus**.

Advantages

- Ketamine can also be administered by **IM injection** even when venous access is difficult.
- Good **analgesia**.
- Useful for **minor orthopedic surgery** (including manipulation of fractures), **minor gynecological surgery** (e.g. D and C), **drainage of abscesses**, **debridement of burns**, **change of dressings**.
Ketamine does NOT interact with GABA receptors; this is in contrast to most IV anesthetics, which exert their primary effect through GABA receptors.

Benzodiazepines

- BZDs include **midazolam**, **lorazepam**, **diazepam**.
- Used for **premedication** (anxiolysis and anterograde amnesia).
- Preferred drugs for **endoscopies**, **cardiac catheterization**, **angiography** and **conscious sedation**.

MAC (MINIMUM ALVEOLAR CONCENTRATION)

Definition

- The lowest concentration of the anesthetic in pulmonary alveoli needed to produce immobility in response to painful stimulus (surgical incision) in 50% individuals.
- **MAC is a measure of the potency:** MAC is **inversely proportional** to potency; i.e. higher the MAC lower is the potency and lower the MAC, higher the potency.

MAC of Some Inhaled Anesthetics

- Nitrous oxide = 105% (**Highest MAC**; **Least potent**)
- Desflurane = 6%
- Sevoflurane = 2.0%
- Ether = 1.9%
- Isoflurane = 1.2%
- Halothane = 0.75% (**second lowest MAC**; very potent)
- Methoxyflurane = 0.16 (**lowest MAC**, **most potent**, **no longer used**)

Contd...

↓ MAC due to

- Increasing age
- Hypothermia
- Concurrent use of opioids
- Acute alcohol ingestion
- Clonidine, Lithium
- Lidocaine

↑ MAC due to

- Infants
- Hyperthermia
- Hypernatremia
- Chronic ethanol abusers
- Increased catecholamine levels in CNS

EXTRA EDGE

- Factors which **do not** affect MAC are thyroid status (hypo/hyperthyroidism) and gender (male/female).
- '**MAC-awake**': Alveolar concentration of anesthetic at which a patient opens his/her eyes to verbal commands (approx = **0.3 MAC**).
- MAC in **infants > neonates > adults**.

BLOOD GAS PARTITION COEFFICIENT

- This is a measure of the **solubility of the inhalation anesthetic in the blood** relative to its solubility in the inspired air; **determines the speed** of induction and recovery. **Newer anesthetics** (such as desflurane) typically have smaller blood-gas partition coefficients than older ones (such as ether); these are preferred because they lead to **faster onset of anesthesia** and **faster emergence** from anesthesia once application of the anesthetic is stopped.
- Blood gas partition coefficients of various agents (lower to higher): Desflurane (0.42) < N₂O (0.47) < Sevoflurane (0.65) < Isoflurane (1.46) < Halothane (2.5).

EXTRA EDGE

- The **potency** of an anesthetic is associated with its **lipid solubility** which is measured by its **oil/gas partition coefficient**.

INHALATIONAL AGENTS AND INTRAVENOUS INFUSIONS

Electrical (EEG) Activity of Inhalational Agents

- Halothane: Typical **biphasic** pattern
- **Isoflurane:** **Isoelectric** EEG
- Desflurane, Sevoflurane: 'Burst suppression' in high dose.
- Nitrous oxide: Both amplitude and frequency increased.

Vapor Pressure and Boiling Point

- **Vapor pressure:** In a closed container, molecules from a volatile liquid escape the liquid phase and become vapor. These gaseous molecules strike the wall of the container and exert vapor pressure. Vapor pressure

is directly proportional to temperature. Increasing temperature will increase the ratio of gas:liquid molecules, thereby increasing vapor pressure.

- **Boilingpoint:** Boilingpoint is defined as the temperature at which vapor pressure equals atmospheric pressure (760 mm Hg).

	Vapor pressure (at 20°C), mm Hg	Boiling point (°C)
Sevoflurane	157	58.5
Desflurane	669	22.8
Isoflurane	238	48.5
Enflurane	172	56.5
Halothane	243	50.2
N ₂ O	38770	88

Ether

- It is **stored in dark bottles** with corks/caps as light may decompose it.
- Ether is **Explosive** when mixed with oxygen and is **inflammable** in air (**do not use with cantery**).
- **Etheromania** refers to ether addiction.

Advantages	Disadvantages
<ul style="list-style-type: none">• Ether stimulates respiration and blood flow due to its sympathomimetic effect mediated by adrenaline release.• It is a branchodilator and produces analgesia; it produces good abdominal muscle relaxation.• Safest anesthetic in unskilled hands —can be given by open drop method.	<ul style="list-style-type: none">• Ether is a/w a slow onset and a slow recovery.• It stimulates salivation (atropine premedication necessary);• Very pungent odor; more nausea and vomiting.

Nitrous Oxide

Pharmacology

- Aka laughing gas
- It is a **colorless, odorless, non-irritant** gas; **good analgesic BUT weak anesthetic** with an MAC of 105.
- **Maximum safe concentration** that can be administered without the risk of hypoxia is **approximately 70%**.
- N₂O is **NOT** metabolized in the body.
- Nitrous oxide is **premixed with oxygen as a 50%: 50% mixture** called '**Entonox**' which is widely used analgesic in obstetrics.
- Induction of inhalational agent is **faster** when combined with nitrous oxide.

Isoflurane**Sevoflurane**

- Popular for use in **day-case surgery**
- **Coronary steal** may occur
- No cardiac dysrhythmias, so **safe in phaeochromocytoma**
- **Agent of choice for neurosurgical anesthesia** (decreases ICT) and in **anesthesia for liver disease**
- Not preferred for induction since **highly irritant**

- Suitable for **day-case surgery** and **in-patient surgery**
- Agent of choice for **face mask induction in children** (less pungent)
- **DO NOT use in closed circuit** since a toxic compound (**Compound A**—PIFE, pentafluoroisopropenyl fluoromethyl ether) is produced
- **Carbon monoxide** production is **least** (when compared with desflurane or isoflurane)

- N₂O causes **NO changes** in CSF production or absorption.
- N₂O causes **increase** in cerebral metabolic rate and cerebral blood flow.

Unique Points about Nitrous Oxide

- **'Diffusion hypoxia' or 'Fink effect' or 'Third gas effect':** At the end of anesthesia, rapid excretion of nitrous oxide into the alveoli dilutes any oxygen present. This can be overcome by **increasing inspired oxygen concentration during recovery** (that is the reason—100% oxygen is giving during recovery!).
- **Paynting effect:** Certain mixtures of nitrous oxide and oxygen will remain in the gaseous phase at pressures and temperatures, at which, nitrous oxide by itself would normally be liquid.
- **Second gas effect** is significant when N₂O is given at 70–80% concentration. However this effect accounts for only a small increase in the concentration of accompanying volatile anesthetic.

Systemic Effects

- It **diffuses more rapidly** into air-filled cavities than any nitrogen can escape causing either a **rise in pressure** (e.g. in the middle ear) or an **increase in volume** (e.g. within the gut of an air embolus). **Contraindicated** in **pneumothorax** and in patients who have been **scuba diving** within the previous 24 hours due to the potential for decompression sickness.
- **Methemoglobinemia**, mainly due to its impurities (Nitric oxide and nitrogen dioxide).
- **Megaloblastic anemia** because nitrous oxide inhibits methionine synthetase; also it may cause **bone marrow suppression**.

Halothane (Fluothane)**Pharmacology**

- Chemical structure contains **fluorine, chlorine and bromine**.
- **MOST extensively metabolized** inhalational anesthetic!
- Colorless, volatile liquid, sweet odor.
- Halothane contains thymol as a stabilizing agent and is **stored in dark amber colored bottles** as it is

decomposed by ultraviolet light. The **vapor is absorbed by rubber**.

- It has **NO analgesic** action. It can be used with soda lime in a circle system.
- Historically, concentration of halothane in gas flow was measured using **Drager Narcotest** (rubber strips); **Riken** gas indicator (light wave interference); **Hook and Tucker** method (UV light); **Bruel and Kjaer** gas monitor and **Engstrom EMMA** vapor analyzer.

Systemic effects of halothane

- ↓ BP and IOP.
- Increases **cerebral blood flow** and the ICT.
- **Arrhythmias:** Sensitizes the myocardium to catecholamines
- **Bradycardia**
- Respiratory depression, but **bronchodilation**.
- Relaxation of skeletal and smooth muscle including the pregnant uterus, which may increase blood loss during cesarean section.
- Shivering ('**halothane shakes**'), and **tremor** are common in the immediate postoperative period following halothane anesthesia.
- Repeated doses of halothane cause hepatotoxicity ('**halothane hepatitis**')—do not use halothane twice within a 6-month period; **20–40% fatality rate** and it can trigger **malignant hyperpyrexia**.

Desflurane

- Desflurane is:
 - 5 times **less potent** than isoflurane
 - **MOST pungent**—hence NOT preferred for induction
 - **NO nephrotoxicity** (NO fluoride ions are produced)
 - Needs **special heated vaporizer**
 - It is a **greenhouse gas** and has **maximum global warming potential**.

EXTRA EDGE

- **Global warming potential:** Desflurane > Isoflurane > Sevoflurane > Nitrous oxide (least) ('**DISNEY!**')

Metabolism of Inhalational Anesthetics

- Order of metabolism from 'Most to Least' = **Methoxyflurane > Halothane > Sevoflurane > Isoflurane > Desflurane > Nitrous Oxide > Xenon** (Inert, NO metabolism).
- Crazy mnemonic! '**Mighty Happy SID NOX**' (may be, SID knocks on your door since he is Mighty Happy for getting a PG seat !!??)

Remember!

- **No analgesia:** Halothane
- **Excellent analgesia** (weak anesthesia): Nitrous oxide
- **Most potent analgesia:** Trilene
- **Pungent agents:** Desflurane (most) > isoflurane

NEUROMUSCULAR BLOCKING DRUGS**Depolarizing vs Nondepolarizing Block**

Characteristic	Depolarizing block (phase 1 block)	Nondepolarizing block (phase 2 block)
Effect on single twitch height	Depression	Depression
Train of four fade	Absent	Present
Tetanic fade	Absent	Present
Posttetanic facilitation	Absent	Present
Effects of anti-cholinesterase agents	Potential of block	Reversal of block
Effect of non-depolarizing drugs	Less blockade	More blockade

DEPOLARIZING MUSCLE RELAXANTS**Suxamethonium (Succinylcholine, Scoline)****Pharmacology**

- It consists of **two molecules of acetylcholine** joined together.
- **Rapid onset** and **Ultra-short acting**; Almost used **exclusively IV**; muscle **fasciculations** are followed by profound relaxation in 40–60 seconds; the rapid onset makes it the **drug of choice to facilitate endotracheal intubation** in patients likely to regurgitate and aspirate.
- It is also used during **modified Electroconvulsive therapy (ECT)**.
- Unlike acetylcholine, suxamethonium is not hydrolyzed by acetylcholinesterase and **depolarization persists for several minutes**, preventing further muscle activity. Ultimately, hydrolysis by **plasma (pseudo-) cholinesterase** occurs, with restoration of normal neuromuscular transmission.
- Shelf life of scoline stored at 2–8 °C is **18 months**.

Systemic Effects of Succinylcholine

- **Cardiac:** **Bradycardia**, junctional rhythm, sinus arrest
- **Fasciculations**
- **Hyperkalemia**
- **Postoperative Myalgia** (neck, back and abdomen) and **Myoglobinuria**
- **Transient rise in ICT and IOP**; Increased IOP may cause loss of vitreous in penetrating eye injuries
- **Increased intragastric pressure**
- **Prolonged apnea** in patients with **inherited plasma pseudocholinesterase deficiency**—abnormal pseudocholesterase can be detected by determining the '**dibucaine number**' in the serum of the individual; Treatment consist of **ventilatory support** until block wears off. (Note **TRUE** cholinesterase is present in nerve endings, RBCs)
- **Malignant hyperpyrexia** in susceptible patients
- **Myasthenia Gravis** patients are **resistant to succinylcholine** BUT **highly sensitive to nondepolarizing muscle relaxants**.
- **Muscular dystrophy** patients are at risk for malignant hyperthermia and dangerous hyperkalemia.
- Prolonged exposure of the neuromuscular junction to succinylcholine can result in (i) desensitization block or (ii) **Phase II block**.

NONDEPOLARIZING MUSCLE RELAXANTS

- These drugs **compete with acetylcholine** and **block its access to the postsynaptic receptor sites** on the muscle but **DO NOT cause depolarization** and are sometimes referred to as **competitive relaxants**.
- **Ocular muscles are the MOST sensitive; diaphragm is the LEAST sensitive muscle**, which is why patients undergoing surgery sometimes hiccup or breathe as an early sign that the relaxants are wearing off. **First affected** are eyelids and neck muscles.

Tubocurarine (Curare)

- **First nondepolarizing relaxant to be used** in clinical practice by Griffiths and Johnson.
- Obtained from the **Amazon region plant chondradendron tomentosum** used as an **arrow poison** by local people.
- It causes **hypotension** secondary to ganglion block and vasodilation, also **causes histamine release**.

Atracurium

- At body temperature and pH, atracurium undergoes spontaneous degradation via '**Haffmann elimination**' and is therefore **stored at 4°C to reduce the rate of spontaneous degradation**; major metabolite is **laudanosine**, which is a **CNS stimulant**

Contd...

Contd...

- It is the **relaxant of choice in patients with hepatic or renal (anephric) dysfunction**
- It is suitable for patients with atypical cholinesterase; O-P poisoning, and in myasthenia gravis
- Its actions will be prolonged in hypothermic patients, e.g. during cardiac surgery
- **Histamine release:** Contraindicated in asthmatics; decreases BP

Cisatracurium

- Purified cis-isomer of atracurium; **more potent** and **slightly longer** duration of action than atracurium
- **Better than atracurium** because **NO histamine release**; provides **greater cardiovascular stability**; Hoffman elimination occurs

Mivacurium

- **Shortest acting** non-depolarizing muscle relaxant; metabolized by plasma **cholinesterase**; rapid recovery, reversal often unnecessary; Useful in **day-case surgery**.

Doxacurium

- **Long acting**; the **most potent neuromuscular blocking drug** currently available; **daxacurium** is **NOT** metabolized by plasma cholinesterase

Vecuronium

- No histamine release; No cardiovascular side effects; **safe** in liver failure; **safe** in renal failure

Rocuronium

Intermediate duration relaxant; **most rapid onset time** - hence used as **alternative to suxamethonium for rapid sequence induction**

Pancuronium

- **Long acting**; **Pulse rate and BP are both increased** (blocks reuptake of norepinephrine), rare histamine release, **useful in asthmatics**.

Pipecuronium

- A **long acting** steroid analog of pancuronium.

Assessment of Neuromuscular Blockade

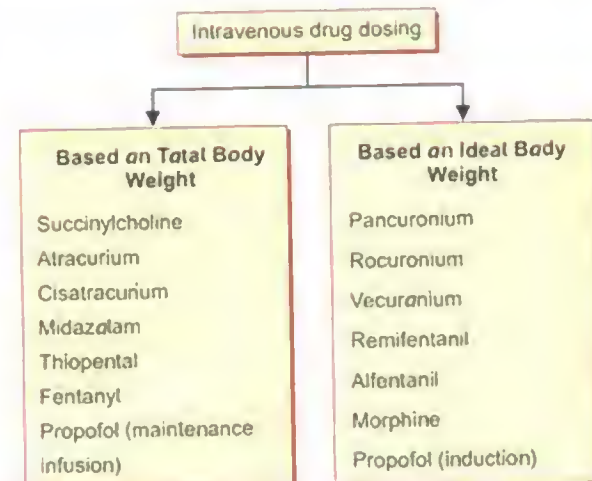
- Assessment of **neuromuscular blockade with non-depolarizing muscle relaxants** is done by stimulating a peripheral nerve (Ulnar nerve supplies adductor pollicis is the preferred nerve) and measuring the response. Types of stimulation (non-tetanic) include—**Train of Four (TOF)** and **double burst stimulation (DBS)**.
- Other method of **monitoring neuromuscular function** include **electromyography, kinemyography** and **acceleromyography**.

EXTRA EDGE

- Neuromuscular blocking drugs are the MC cause of anaphylaxis in the immediate postoperative period.
- **Sugammadex** is a **selective relaxant binding agent** that provides **rapid reversal** from neuromuscular blockade induced by the nondepolarizing neuromuscular blocking agents **rocuronium**.

IV Drug Dosing Based on Different Types of 'Body Weight'

- **Total Body Weight (TBW)** = Body weight recorded when we stand on a weighing scale.
- **Ideal Body Weight (IBW)** is calculated based on **gender and height**.
 - IBW tells you what weight a person 'should actually be' to be associated with **maximum life expectancy for a given height** (it was originally derived from information collected by the life insurance industry!)
 - $IBW (Kg) = Height (cm) - 100 (male) \text{ or } 105 (female)$.
- **Lean Body Weight (LBW)** = TBW - Fat Mass.
- These measurements are useful for **drug dosing** in **morbidly obese patients**. Even though these patients have increased body fat, the majority of cardiac output is still directed to fat free tissue (lean tissue). Therefore dosing a drug based on total body weight in the morbidly obese may result in overdose.

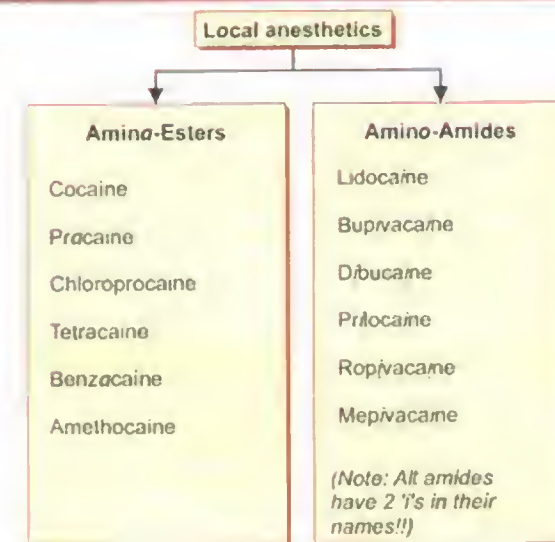
**RAPID SEQUENCE ANESTHESIA**

- The objective of rapid sequence anesthesia (RSA) is to secure the airway rapidly and **prevent the aspiration of gastric contents**.
- Steps are
 - Prepare equipment

- **Premedications** are **NOT** usually given (no evidence from literature);—however if used, lidocaine (for head injury) and atropine for children (prevents bradycardia).
- **Preoxygenation** for full 3 minutes.
- **Paralysis and induction:** IV induction agent **Propofol** or etomidate (avoid in septic patients) and neuromuscular blocking agent **Succinylcholine** (scoline) or **rocuronium** is given.
- **Sellick's maneuver (cricoid Pressure)** is done to prevent aspiration.
- Intubate with cuffed endotracheal tube and the establish lung ventilation.
- **NOT DONE:** **mask ventilation** before intubation is avoided.

Remember!

- Shortest acting NDMR : Mivacurium
- Most potent NDMR : Daxacurium
- Fast acting NDMR : Rocuronium
- MR of choice in renal/hepatic failure: Atracurium

LOCAL ANESTHETIC AGENTS**Basic of LA**

- **Mechanism of action** of LA's = blockade of **membrane depolarization** at voltage gated **sodium channels**.
- **Topical (surface) anesthetics:** Lidocaine; tetracaine; dibucaine, prilocaine, cocaine.
- **Amides** are **more longer acting** than esters.
- **Alkalinized** solutions (addition of sodium bicarbonate) of local anesthetic causes increase in the non-ionized form and has following advantages:

- **Less painful** injection
- **Faster onset** of action
- **Improves quality of block**
- **Differential blockade:** Local anesthetics have the ability to produce varying degrees of inhibition for sensory and motor activity. For example
 - Bupivacaine and ropivacaine exhibit a more potent sensory than motor block
 - Etidocaine exhibits an equally effective sensory and motor block.

More about LAs

- Order of blockade of nerve fibers by LAs:
 - Least to most susceptible: Small myelinated fibers ($A\delta > A\gamma > A\beta > A\alpha > B > C$)
- **Uptake (rate of absorption) of local anesthetic** from greatest to least is as follows:
 - IV > tracheal > intercostal > caudal > paracervical > epidural > brachial > sciatic > subcutaneous

Lignocaine (Lidocaine)

- Most widely used LA; very **versatile agent** used for **local, spinal, epidural, IV regional anesthesia**.
- It is not used orally due to **extensive first pass metabolism**
- Used as RH
 - 1% and 2% injection (with or without adrenaline)
 - **2% jelly**
 - **4% topical solution**
 - **5% (heavy)** for spinal anesthesia
- Also used IV in **cardiac arrhythmias**—it selectively blocks Na^+ channels in their open and inactive states.

Bupivacaine

- Widely used in **obstetric analgesia**, both **spinally and epidurally**. It has a long duration of action lasting up to 10 hours after a nerve block.
- **MOST cardiotoxic local anesthetic: DO NOT** use for **IV regional anesthesia**—**refractory cardiac arrest** may occur (binds to **sodium channels** in **systole**).
- **Levobupivacaine** has **reduced cardiotoxicity**.

Prilocaine

- It is the **agent of choice for IVRA (Bier's block)**.
- In overdose its metabolite (o-tolidine) can cause **methe-moglobinemia**
- Treat with **methylene blue** IV.

EMLA

- This is an *eutectic mixture of lignocaine 2.5% and prilocaine 2.5%* (equal proportions). Applied as a *cream to the skin* it produces surface analgesia in approximately 60 minutes.
- *Eutectic* means having a low melting point, below that of either compound separately.
- Used to *reduce pain of IV cannulation in children*; also been used for *split-skin grafts, removal of anal warts and postherpetic neuralgia*.

Vasoconstrictors

- These are added to local anesthetics to *reduce the rate of absorption, reduce toxicity and extend their duration of action*. Two drugs used for their vasoconstrictor properties are *adrenaline and felypressin*.
- Local anesthetics containing vasoconstrictors must NEVER BE USED AROUND EXTREMITIES (e.g. fingers, toes, penis), as the vasoconstriction can cause fatal tissue ischemia.

Felypressin

This is a *synthetic compound* related to vasopressin with ONLY vasoconstrictor properties. It is MC used in conjunction with prilocaine.

Maximum Recommended Doses

	Plain	With adrenaline
Lignocaine	3 mg/kg (max 200 mg)	7 mg/kg (max 500 mg)
Bupivacaine	2 mg/kg	2 mg/kg

EXTRA EDGE

- Concentration of adrenaline used with lidocaine is **1:200,000 (5 mcg/mL)**.
- Addition of adrenaline to LA: *Reduces systemic toxicity* of LA; provides *bloodless field* for surgery and *prolongs duration of action of LA*.
- Earliest sign of systemic absorption of local anesthesia is circumoral numbness.

More about Local Anesthetics (LA)

- Cocaine is a (*vasoconstrictor*)—hence *contraindicated with adrenaline*
- *Prilocaine*: First synthetic LA
- *Dibucaine*: *Most potent, most toxic, longest acting LA*.

Opioid Analgesics

Morphine	<ul style="list-style-type: none"> • IM or IV; also SC, epidurally, rectally, intrathecally; effective against visceral and myocardial ischemic pain
Fentanyl	<ul style="list-style-type: none"> • 100 times as potent as morphine; used IV • Popular in cardiathoracic surgery because of the cardiovascular stability; ventilatory support needed immediately postoperatively • May cause chest tightness during induction—wooden chest syndrome
Alfentanil	<ul style="list-style-type: none"> • Only one-fifth as potent as fentanyl • Used as IV bolus for short procedures • Its short duration of action makes it popular in day-case patients • Causes profound respiratory depression
Sufentanil	<ul style="list-style-type: none"> • 6–7 times greater potency than fentanyl • Shorter duration of action
Remifentanyl	<ul style="list-style-type: none"> • An ultra-short acting, mu-opioid receptor agonist for major procedures • Very rapid recovery BUT profound respiratory depression • Widely used in Total IV Anesthesia (TIVA)

ANESTHESIA AT HIGH ALTITUDE

- In *anesthesia at higher altitudes*, the partial pressure remains the same, but the concentration of drug required for anesthesia increases.
- There is *increased risk of*:
 - Perioperative hypoxia
 - Volume overload (with fluid resuscitation)
 - Increased blood loss (due to high venous pressure and increased volume)
 - Hyperthermia.

HYPOTHERMIA AND ANESTHESIA

- Mild inadvertent core hypothermia commonly occurs in general anesthesia and in neuraxial anesthesia also.
- Main route of heat loss during anesthesia is by '*radiation*'.
- The 'gold standard' for measuring core temperature is the temperature of '*pulmonary arterial*' blood BUT safe, easily accessible and accurate site for measuring core temperature is the '*distal esophagus*'.
- Other sites reflecting core temperature are *tympanic membrane* and *nasopharynx* (rectal temperature is NOT reliable).
- '*Adverse effects*' of hypothermia:
 - Increased perioperative blood loss/coagulopathy
 - Increased post-op recovery time due to altered drug metabolism

- Delayed wound healing
- Increased rates of surgical wound infection
- Increased cardiac morbidity including myocardial ischemia, arrhythmias
- Postoperative shivering and increased oxygen consumption.
- Beneficial effects of hypothermia:
 - *Therapeutic hypothermia* has been used in *neurosurgery and CABG* since hypothermia protects against tissue hypoxia and ischemia.
- Prevention
 - Using forced air warmers
 - Warm IV fluids
 - Maintain higher OT ambient temperature.

THERAPEUTIC USES OF CO₂

- *Laparoscopic surgery* involves insufflation of a gas (*usually carbon dioxide*) into the peritoneal cavity producing a pneumoperitoneum
- A very effective way to *minimize air embolism during cardiac surgery* is to *flood the operative field with CO₂*
- *Debubbling*—Generally, a 100% CO₂ flush of the arterial line filter, membrane oxygenator, and tubing for several minutes is used to remove all room air from the bypass circuit
- *Carbogen*, (aka *Meduna's Mixture*) is a mixture **95% oxygen and 5% carbon dioxide**; it can be used as part of the early treatment of *central retinal artery occlusion and in radiotherapy to overcome radioresistance*
- To *facilitate vasodilation* and thus lessen the degree of metabolic acidosis during the induction of *hypothermia*
- To *prevent hypocapnia during hyperventilation*
- For clinical and physiological investigations
- In *gynecological investigation* for *insufflation into fallopian tubes and abdominal cavities*
- As *solid carbon dioxide (dry ice)* in *tissue freezing techniques* and for the *destruction of warts by freezing*
- To *increase cerebral blood flow* in arteriosclerotic patients undergoing surgery
- To stimulate respiration after a period of apnea
- In chronic respiratory obstruction after it has been relieved
- To increase depth of anesthesia rapidly when volatile agents are being administered. It increases depth of respiration and helps to overcome breath holding and bronchial spasm
- To facilitate blind intubation in anesthetic practice.

MALIGNANT HYPERTHERMIA (MH)

- Pathogenesis
 - MH is an inherited myopathy characterized by a hypermetabolic state after exposure to an appropriate triggering agent. A defect at the sarcoplasmic reticulum leads to *decreased calcium reuptake*. Specifically, the *ryanodine receptor* (a calcium release channel) *fails*, and *intracellular calcium increases 500-fold*, leading to a *sustained muscle contractions, glycolysis, and heat production*.
- Drugs causing MH
 - *Succinylcholine*, gallamine, halothane, isoflurane, enflurane, sevoflurane, desflurane, methoxyflurane, lidocaine, mepivacaine, trichloroethylene, and ethyl chloride, ethylene, diethyl ether.
- Drugs safe in patients susceptible to MH
 - N₂O, thiopentone, benzodiazepines, barbiturates, local anesthetics, nondepolarizing muscle relaxants, *propofol*.
 - *Ketamine and pancuronium should be used with caution* in MH susceptible patients, because the resulting tachycardia may mask the onset of MH.

Presentation of MH

- First sign: Unexplained **tachycardia**
- **Tachypnea** in spontaneously breathing patients
- **Muscle rigidity**, despite the use of relaxants
- Failure to relax after suxamethonium
- Cardiac dysrhythmias
- A falling oxygen saturation and cyanosis
- An increased end-tidal CO₂
- Labile BP
- MH may go unnoticed unless the patient's temperature is being monitored

Diagnosis

- Analysis of the arterial blood sample will demonstrate a *profound metabolic acidosis* (low pH and bicarbonate), a *low PaO₂ and high PaCO₂*.
- Continued muscle contraction results in *hyperkalemia* and *myoglobinuria* causing renal failure. DIC may develop.
- The *gold standard of diagnosis is the caffeine halothane contraction test* performed on muscle obtained by biopsy.

Treatment

- *Dantrolene IV* is used for treatment. Bromocriptine may also be used.

MECHANICAL VENTILATION

- Mechanical ventilation is a therapeutic method that is used to *assist or replace spontaneous breathing*.
- Indications are
 - **Hypoxemic respiratory failure (MC indication):** acute respiratory distress syndrome, heart failure with pulmonary edema, pneumonia, sepsis, complications of surgery and trauma); arterial O₂ saturation (SaO₂) <90% occurs despite an increased inspired O₂ fraction.

Modes of Mechanical Ventilation

Mode	Advantages	Disadvantages
ACV	Patient control Guaranteed ventilation Most widely used method	Potential to hyperventilate Barotrauma and volume trauma Every effective breath generates a ventilator volume
IMV	<ul style="list-style-type: none">• Patient control• Comfort from spontaneous breaths• Guaranteed ventilation	<ul style="list-style-type: none">• Potential dyssynchrony• May result in hypoventilation
PSV	<ul style="list-style-type: none">• Patient control• Comfort• Assures synchrony	<ul style="list-style-type: none">• No timer backup• May result in hypoventilation
NIV	<ul style="list-style-type: none">• Patient control	<ul style="list-style-type: none">• Mask interface may cause discomfort and facial bruising• Leaks are common hypoventilation
CMV	<ul style="list-style-type: none">• Ventilator delivers a preset number of breaths/min of a preset volume• Additional breaths cannot be triggered by the patient• Used in patients who are paralyzed	

Key: ACV = Assist control ventilation; IMV = Intermittent mandatory ventilation; PSV = Pressure support ventilation; NIV = Noninvasive ventilation; CMV = Controlled mechanical ventilation.

Positive End Expiratory Pressure (PEEP)

- PEEP is the maintenance of positive pressure within the lungs at the end of expiration (positive end expiratory pressure)
- In spontaneous ventilation using noninvasive ventilation (NIV) the equivalent is CPAP (continuous positive airway pressure)
- During Positive End Expiratory Pressure (PEEP) in ARDS, the pressure of **12-15 mm Hg** is a theoretical '*optimal PEEP*' for alveolar recruitment.

Advantages	Disadvantages
<ul style="list-style-type: none">• ↑ Airway pressure• ↑ FRC and residual volume (prevention of airway collapse)	<ul style="list-style-type: none">• Impaired CO₂ elimination; ↑ pulmonary vascular resistance (PVR); dead space (PA > Pa > Pv); ↑ Alveolar-arterial gradient; ↑ ICP

Contd...

Advantages	Disadvantages
<ul style="list-style-type: none">• ↑ PaO₂; ↓ airway resistance; ↓ V/Q mismatch; Improved distribution of inspired gas• ↓ Work of breathing; prevention of surfactant aggregation reducing alveolar collapse; ↓ in LV afterload	<ul style="list-style-type: none">• May worsen right to left Intracardiac shunt by PVR; ↓ cardiac output; ↓ LV compliance (due to intraventricular septum displacement)• ↓ Urine output through increased ANP; ↓ GFR and increased ADH (sodium retention)• ↓ Hepatic artery and portal venous flow (liver congestion); ↓ peribronchial lymphatic flow; ↓ splanchnic blood flow

Contd...

- **Hypercarbic respiratory failure** (coma, exacerbations of chronic obstructive pulmonary disease, and neuromuscular diseases); arterial PCO₂ values >50 mm Hg.
- Two methods for ventilating patients:
 - **Noninvasive Ventilation** (NIV—tight fitting face mask or nasal mask); **MC used in acute exacerbation of COPD.**
 - **Invasive Ventilation or Conventional Mechanical Ventilation** (MV—with cuffed endotracheal intubation).

Methods for Improving Oxygenation During Ventilation

- Prone positioning
- Inverse ratio ventilation (inspiratory time > expiratory time)
- High frequency jet ventilation
- High frequency oscillatory ventilation (HFOV)
- Extracorporeal membrane oxygenation (ECMO)
- Airway pressure release ventilation (APRV)
- Partial liquid ventilation (PLV) using perfluorocarbons
- Inhaled nitric oxide.

Ways to Increase Mean Airway Pressure During Ventilation

- Increase rate of inspiratory flow
- Increase the PEEP
- PIP (peak inspiratory pressure) can be increased
- Inspiratory time can be lengthened and expiratory time can be shortened.

Weaning (Withdrawal of) Mechanical Ventilation

Spontaneous breathing trial for 30-60 minutes may be tried using:

- CPAP (continuous positive airway pressure)
- PSV (pressure support ventilation)
- SIMV (Synchronized intermittent mandatory ventilation)
- T-tube technique.

CARDIOPULMONARY RESUSCITATION

As per latest guidelines (AHA 2015 Guidelines)—

- 'CAB' is followed, (**not** ABC)—i.e. Circulation, Airway and Breathing—i.e. immediately begin **chest compressions** rather than opening the airway.
- To **allow full chest wall recoil** after each compression, rescuers must **avoid leaning on the chest between compressions**.
- Rescuer should **NOT interrupt compression** for > **10 seconds**.
- For patients with **ongoing CPR and an advanced airway** in place, a simplified ventilation rate of **1 breath every 6 seconds (10 breaths per minute)** is recommended.
- The routine use of the **impedance threshold device** (ITD) as an adjunct to conventional CPR is **NOT** recommended.

- In ACLS, (Advanced Cardiac Life Support), vasopressin does not offer an advantage over the use of **epinephrine** alone. Therefore, **vasopressin has been removed** from the Adult Cardiac Arrest Algorithm—2015 update. In 2010 update **atropine was removed**. (Earlier **vasopressin** was recommended as an **alternative to epinephrine**).
- Low end-tidal carbon dioxide (ETCO₂) in intubated patients **after 20 minutes of CPR** is a/w a very low likelihood of resuscitation.
- **Emergency coronary angiography** is recommended for **all patients with ST elevation** and for hemodynamically or electrically unstable patients without ST elevation for whom a cardiovascular lesion is suspected.
- During adult **CPR** tidal volumes of **600 mL** (6 to 7 mL/kg) should be adequate to cause the chest to rise.
- During airway management in an unconscious trauma patient with possible **cervical injury**, **neck hyperextension** should be **avoided**.
- The **most widely used waveform** in the automated electrical defibrillators (AED's) now is the **biphasic truncated exponential** (BTE) waveform.
- The following **drugs** may be given through the **endotracheal tube** during CPR: **Naloxone**, **Atropine**, **Vasopressin**, **Epinephrine** and **Lidocaine** ('**NAVELL**'). (Amiodarone and Sodium bicarbonate are **NOT** given endotracheally).
- However, atropine is **NOT** recommended for routine use in the management of pulseless electrical activity/asystole and has been removed from the ACLS cardiac arrest algorithm (epinephrine, vasopressin and amiodarone are used).

	Adult (> 12 years)	Child (1-12 years)	Infant (< 1 year)
Compression depth	At least 2 inches (5 cm, BUT NOT > 2.4 inches/6 cm)	About 2 inches (5 cm; 1/3 of chest depth)	About 1.5 inches (4 cm, 1/3 of chest depth)
Compression: Ventilation ratio	30:2 (one or two rescuer CPR)	30:2 (single rescuer) OR 15:2 (two rescuers)	
Compression rate	100-120/min		

BLOOD AND BLOOD PRODUCTS

Summary of Blood Groups

Group	Erythrocyte antigens	Antibodies
O	Nil	Anti-A, Anti-B (<i>universal dOnOr</i>)
A	A	Anti-B
B	B	Anti-A
AB	AB	Nil (<i>Universal recipient</i>)

EXTRA EDGE

- **Karl Landsteiner** discovered ABO blood group system in 1901.
- **ABO system** of blood grouping is an example of **codominance**.

Cross matching is the final compatibility test between donor and recipient.

- Major cross matching: The *donor's RBCs* are cross matched with the *recipient (patient's) serum*; most important test
- Minor cross matching: The recipient's RBCs are cross matched with the donor's serum; the main function is to confirm that the original ABO typing of donor and recipient was done correctly.

Storage of Blood

- When blood is stored in liquid state there is
 - Loss of viability of RBCs
 - Loss of red cell ATP
 - **Depletion** of 2,3-DPG
- Whole blood and packed RBCs are stored at 2–6°C
- To preserve RBC function during storage, below additive solutions are used and whole blood can be stored for more days.

Additive to blood	Storage time
ACD (Acid-Citrate Dextrose)	21 days
CPD-A (citrate, phosphate, dextrose-adenine)	35 days
SAGM (saline, adenine, glucose, mannitol)	42 days

Blood and Blood Products

Whole blood
<ul style="list-style-type: none"> • Indicated when patient has lost more than 25% blood volume (e.g. a/w shock) • One unit contains 500 mL of anticoagulated blood per bag with a hematocrit of 40% • No functioning platelets after 2–3 days; ↓ 2,3-DPG by 2 weeks • Normal concentrations of albumin and clotting factors, except factors V and VIII, which are reduced to 10–20% of normal • Not sterilized, so there is a risk of transmitted pathogens

Contd

Contd...

Red Cell Concentrate (Packed RBCs)

- Indicated for **increasing oxygen-carrying capacity in anemic patients** and **increase blood volume in significant hemorrhage**
- **1 unit = 250–300 mL** with a **hematocrit of 70%** and **200 mg iron**; and is given during 2–3 hours
- **1 unit** of packed red cells will increase the **hematocrit by 3%** and **hemoglobin by 1 g/dL** in the average adult
- **No plasma and no functioning platelets.**

Leukocyte-reduced RBCs

- Indicated for patients with a **history of previous febrile transfusion reactions**

Washed RBCs

- Donor cells are processed with normal saline to remove the donor serum as much as possible
- **MC used in IgA deficiency** (to avoid anaphylaxis) and also in **paroxysmal nocturnal hemoglobinuria (PNH)** to deplete complement

Gamma irradiated blood

- For **destruction of donor T lymphocytes** to prevent graft versus host disease in **stem cell transplant patients** and **severely immunocompromised patients**.

Fresh Frozen Plasma (FFP)

- FFP is the fluid portion of human blood that is prepared by separating plasma from RBCs and **frozen within 6 hours of donation**.
- Contains all **clotting factors, antibodies from donor (albumin and gammaglobulin)** and **donor's WBCs**.
- Must be **ABO compatible** and Rh (D)-negative if recipient is a Rh (D) fertile female.
- Risk of **anaphylactic reactions** is present.
- FFP is an acellular component and **DOES NOT** transmit infections, e.g. CMV.

Indications for FFP transfusion

- Urgent **reversal of warfarin** therapy
- Severe **DIC**
- Bleeding due to **multiple clotting factor deficiency** (due to liver disease).

Cryoprecipitate

- Cryoprecipitate forms when the plasma that is separated from fresh whole blood is rapidly frozen and then allowed to rewarm.
- It contains **large quantities of factor VIII, von Willebrand factor, fibrinogen, fibronectin and factor XIII.**

- **Fumate**: A specific **von Willebrand factor** containing **factor VIII concentrate**.

Indications for the use of cryoprecipitate

- In bleeding patients with **von Willebrand disease** and **disseminated intravascular coagulation (DIC)**.
- **Fibrinogen deficiency**.
- Treating hemophilia A.

Platelets

- Indicated for treatment of **thrombocytopenia**.
- During surgery, **platelet transfusion** are required **only** if platelet count < **50,000 cells/mm³**.
- The administration of **1 unit of PC** should increase the platelet count by **5000–8000/m³**.
- **Bacterial contamination** is **most likely** to occur in **platelet concentrates** (since platelets are stored at 20–24°C).
- **Platelets** have **shortest shelf life** of **5 days** (**granulocytes** only have 24 hours shelf life).

Shelf Life of Blood Products

Blood product	Shelf life
Granulocytes	24 hours
Platelets	5 days at 20–24°C (room temperature)
Cryoprecipitate	2 years at minus 20°C
Fresh Frozen Plasma (FFP)	2 years at minus 40–50°C

PLASMA/BLOOD VOLUME REPLACEMENT SOLUTIONS

Crystalloids

- A substance with properties of a crystal; aqueous fluids containing dissolved sugars or salts.
- Replacement volume is about **three times** that of blood loss because of distribution to the extracellular space; has only a transient effect.

Isotonic crystalloids	
Normal saline	(0.9% NaCl): Iso-osmotic, pH is 5.5 (acidic , lower than plasma pH of 7.4); mild hypernatremia and hyperchloremia with large volumes
Hartman's solution (Ringer Lactate)	Contains sodium, potassium, calcium, chloride, lactate

Contd

Contd...

Hypotonic crystalloids

Half normal saline + Dextrose	0.45% NaCl + Dextrose 2%
Dextrosaline	0.18% NaCl + Dextrose 4%; use stopped in children due to hyponatremia
5% dextrose	
50% dextrose	Used in emergency management of hypoglycemia and given along with insulin for treating hyperkalemia

Hypertonic crystalloids

Hypertonic saline	7.5% NaCl; risk of central pontine myelinolysis
-------------------	--

Colloids

- A colloidal fluid is a dispersion of small particles in a continuous fluid phase, which exert an osmotic effect because the endothelium is relatively impermeable to the colloid particles.
- Replacement volume **equal to** that of blood lost; **colloids** have **higher Na⁺ concentration** than normal saline.

Human plasma derivatives

Human albumin solution (5% or 25%)	Overhydration; pulmonary edema , particularly with use of 25% solution, due to absorption of interstitial fluid into the vascular compartment
------------------------------------	--

Semi-synthetic colloids

Gelatins	<ul style="list-style-type: none"> • Gelofusine (succinylated gelatin) and Hemaccel (polygeline urea linked) • Derived from bovine collagen; highest risk of anaphylactoid reactions
Dextrans (40 or 70)	<ul style="list-style-type: none"> • Potential for anaphylaxis • Interference with platelet, red cell function, and blood cross matching
Starches	<ul style="list-style-type: none"> • Hydroxyethyl starch (Hetastarch, Hespan), Pentastarch (Haes-steril) and Tetrastarch (Voluven) • Affects coagulation, a/w pruritus

TRANSFUSION REACTIONS

Acute

- **Hemolysis, Fever, Anaphylaxis.**
- **Hyperkalemia**—Stored blood is high in K⁺. Effects of additional K⁺ are exacerbated by acidosis and hyperthermia. Hyperkalemia is usually transient.

- **Citrate toxicity**—Citrate is added as a preservative to bind excess calcium and prevent clotting. Metabolized to bicarbonate. Excess causes metabolic alkalosis.
- **Acid-base disturbance**—Citrate from preservative and lactate from red cells.
- **Hypocalcaemia**—Citrate anticoagulant binds ionized calcium; BP, pulse pressure. Give CaCl_2 only if there are symptoms/signs (not Ca^{2+} gluconate, which must be metabolized to release free Ca^{2+}).

Transfusion-related acute lung injury (TRALI)

- **MC** cause of **transfusion-related death**; MC a/w **FFP** transfusion.
- Occurs during or acute (**within 6 hours**) of transfusion.
- It has been a/w **allogeneic antibodies in the donor plasma**; more risk with **multiparous female donors**.
- Usage of **only male** plasma donors and use of fresher blood (<14 days) decreases the risk of TRALI.
- Clinical features: **Non-cardiogenic pulmonary edema** with **hypoxemia** (< 90% oxygen saturation), **dyspnea**, tachypnea, fever and hypotension.
- **Pulmonary vascular sequestration of neutrophils** with leucopenia occurs; **pulmonary edema fluid has high protein** content.
- **CXR**: **Fluffy bilateral interstitial alveolar infiltrates**; cardiomegaly and pleural effusions are **absent**.
- Treatment: **Supportive**; supplemental **oxygen** therapy; severe forms may require **mechanical ventilation** in ICU; majority **recover within 72–96 hours** with no sequelae. **NO** role for diuretics or corticosteroids. **Mortality** is 5–10%.
- **Microemboli**—aggregates of all cellular components, increase with age of blood. Cause complement activation, hemolysis and thrombocytopenia. Removed by 170 mm filter; +/- 40 mm screen and depth filters.
- **Hypothermia**—left shift of O_2 dissociation curve, platelet and clotting dysfunction.
- **Air embolus, fluid overload**.

Delayed

- **Hemolytic transfusion reaction**—from red cell antibodies
- **Graft-versus-host disease**
- **Alloimmunization** (reaction to minor foreign antigens)— 10% of all transfusion reactions: Red cell antibodies including anti-Rh (D); Leucocyte antibodies; Platelet antibodies.

Infections transmitted by blood transfusion

- **Viral infection**—HIV, hepatitis C, West Nile Virus, hepatitis B, CMV, HTLV, parvovirus (causes aplastic anemia in sickle cell patients).
- **Other infections**—Syphilis, Malaria, Trypanosomiasis (Chaga's), variant Creutzfeldt Jakob disease.

- **Tumor recurrence**—increased risk
- **Sensitization**—resulting in antibody formation and subsequent difficulties with cross-matching
- **Iron overload**—occurs with repeated transfusions.

'Jehovah's Witnesses'

'For the life of the flesh is in the blood: and I have given it to you upon the altar to make atonement for your souls: for it is the blood that maketh an atonement for the soul. Therefore I said unto the children of Israel, No soul of you shall eat blood, neither shall any stranger that sojourneth among you eat blood' (Leviticus 17:10-12; see also Genesis 9:3-4 and Acts 15:28-29).

Jehovah's witnesses are a group of people who **refuse administration of all blood products**. However, they may allow blood to be retransfused if it has not lost contact with the circulation, e.g. cardiopulmonary bypass.

PHYSICS

Gas Laws	
• Charles's law	The volume of a given mass of a gas is directly proportional to absolute (Kelvin) temperature at constant pressure
• Boyle's law	The volume of a given mass of a gas is inversely proportional to pressure if at constant temperature
• Gay-Lussac's law	At constant volume, the absolute pressure of a given mass of gas varies directly with the absolute pressure
• Graham's law	Rate of diffusion $\propto 1/\text{molecular weight}$
• Henry's law	Amount of gas dissolved \propto partial pressure of the gas
• Fick's law	Rate of diffusion across a membrane \propto concentration gradient
• Adiabatic change	A change in pressure, volume or temperature without change in energy of a gas (i.e. heat is lost or added)
• Avogadro's hypothesis	Equal volumes of 'ideal' gases at the same temperature and pressure contain the same number of molecules (Avogadro's number 6.022×10^{23} molecules occupying 22.4 L at STP).

Pressure	
• Dalton's law of partial pressures	The pressure exerted by a mixture of gases is equal to the sum of the pressures, which each gas would exert on its own

Contd...

Contd...

Solubility															
• Ostwald solubility coefficient	The amount of gas that dissolves in a unit volume of liquid under the stated temperature and pressure														
• Bunsen solubility coefficient	The amount of gas that dissolves in unit volume of a liquid at standard temperature (273K) and pressure (101.3 kPa)														
• Meyer Overton rule	States that the potency of anesthetic gases is proportional to their lipid solubility (olive oil solubility)														
Temperature															
• Critical temperature	Temperature above which a gas cannot be liquified.														
	<table><tr><th>Gas</th><th>Critical temperature (Deg C)</th></tr><tr><td>Oxygen</td><td>- 119</td></tr><tr><td>Nitrogen</td><td>- 140</td></tr><tr><td>Air</td><td>- 125</td></tr><tr><td>N_2O</td><td>36.5</td></tr><tr><td>CO_2</td><td>31.1</td></tr><tr><td>Cyclopropane</td><td>124.4</td></tr></table>	Gas	Critical temperature (Deg C)	Oxygen	- 119	Nitrogen	- 140	Air	- 125	N_2O	36.5	CO_2	31.1	Cyclopropane	124.4
Gas	Critical temperature (Deg C)														
Oxygen	- 119														
Nitrogen	- 140														
Air	- 125														
N_2O	36.5														
CO_2	31.1														
Cyclopropane	124.4														
• Critical pressure	Pressure above which a gas at its critical temperature cannot be liquified.														
• Pseudocritical temperature	Temperature at which a mixture of gases separate out into their separate components, e.g. N_2O and O_2 in Entonox at -5.5°C														
• Specific heat capacity	Amount of heat required to increase the temperature of a substance by $1^\circ\text{C}/\text{kg}$														
Gas Flow															
• Bernoulli effect	Fall of pressure at a constriction in a tube. Increased gas/fluid velocity results in increased kinetic energy with a reduction in potential energy and thus a decrease in pressure														
• Coanda effect	Streaming of a gas at a division in tubing along only one of the divisions. Used as logic valve in some ventilators														
• Poynting effect	A mixture of gases (e.g. Entonox) remains in a gaseous state, even though one component (N_2O) would normally be liquid at high storage pressures														
Humidification															
• Absolute humidity	Is the mass of water vapor present in a given volume of air.														
• Relative humidity	Is the ratio of the mass of water vapor to the mass of water vapor when fully saturated, expressed as a percentage.														

Names of Some Types of Anesthesia

- **Audio anesthesia**: Anesthesia by sound.
- **Basal anesthesia**: A level of unconsciousness that is just above the level of complete surgical anesthesia. The patient does not respond to verbal stimuli but does react to noxious stimuli, such as a pinprick. Basal anesthesia is useful in combination with local or regional anesthesia, making the patient unaware of the surgical experience.
- **Bulbar anesthesia**: Anesthesia produced by a **lesion of the pons**.
- **Anesthesia dolorosa**: Pain in an anesthetised zone, as in **thalamic lesions**.
- **Electric anesthesia**: Anesthesia induced by the use of an **electric current**.
- **Gwathmey's anesthesia**: Anesthesia induced by **injection of an olive oil and ether** solution into the rectum.
- **Hysterical anesthesia**: Bodily anesthesia occurring in **conversion disorders**.
- **Intratracheal anesthesia**: Anesthesia administered through a catheter passed to the level of the trachea.
- **Mixed anesthesia**: General anesthesia produced by more than one drug, such as propofol, for induction followed by an inhaled drug for maintenance of anesthesia.
- **Neuroleptic anesthesia**: General anesthesia produced by a neuroleptic agent such as **droperidol with fentanyl**.
- **Open anesthesia**: Application, usually by **dropping**, of a **volatile anesthetic agent onto gauze** held over the nose and mouth.
- **Pudendal anesthesia**: A type of local anesthesia used in obstetrics. The pudendal nerve on each side, near the spinous process of the ischium is blocked.
- **Rectal anesthesia**: General anesthesia produced by introduction of an anesthetic agent into the rectum used especially in managing pediatric patients.
- **Refrigeration anesthesia**: Anesthesia induced by lowering the temperature of a body part to near freezing either by **spraying it with ethyl chloride** or by **immersing it in a container of finely cracked ice**. SYN: ice anesthesia.
- **Saddle block anesthesia**: A type of anesthesia produced by introducing the anesthetic agent into the **fourth lumbar interspace**. This anesthetizes the perineum and the buttocks area.
- **Segmental anesthesia**: Anesthesia due to a pathological or surgically induced lesion of a nerve root.

- **Splanchnic anesthesia:** Anesthesia produced by injection of an anesthetic into the splanchnic ganglion.
- **Tumescent anesthesia:** The injection of large volumes of diluted lidocaine, bicarbonate, and epinephrine subcutaneously for use in local anesthesia. This procedure is most often used prior to **liposuction** to limit blood loss and pain.
- **Phenylephrine is the vasopressor of choice** to restore coronary perfusion pressure in patients with severe **aortic stenosis** when under **general anesthesia**.
- If there is **bronchospasm or wheezing** during surgery, **deepen the plane** of anesthesia.
- **Dexmedetomidine** is an α_2 adrenoceptor agonist that may cause bradycardia and hypotension.
- **Inhaled nitric oxide** is used in **pulmonary hypertension** in newborn.

MORE HIGH YIELD POINTS

- **Mendelson syndrome** or peptic pneumonia refers to acute **chemical pneumonitis** caused by the **aspiration** of stomach contents in patients under **general anesthesia**, especially **during pregnancy**.
- Current recommendation of **Nil Per Orally (NPO) or Nil By Mouth (NBO)** to **prevent aspiration** is
 - 6 hours for solid food and formula/cow's milk
 - 2 hours for clear fluids
 - 3 hours for breast milk
- **Vital signs** are—pulse/heart rate; respiration rate; BP; temperature. **Pain** is considered as a '**fifth**' vital sign.
- The 6 A's of **premedication**: Anxiolysis, Amnesia, Anti-emetic, Antacid, Anti-autonomic, Analgesic
- The **Clark electrode** measures the PO_2 in the blood sample.
- The **Severinghaus electrode** measures the PCO_2 in the blood sample.
- **Massive Blood Transfusion:** Defined as **replacement of the patient's total blood volume within 24h** OR transfusion of **> 10 units of blood/20 units of RBCs** within 24 hours or replacement of more than 50% of blood volume within 3 hours.
- **Ondine's curse: Idiopathic alveolar hypoventilation syndrome.** It is a condition in which spontaneous ventilation occurs only with voluntary effort and ceases during periods of inattention to breathing or sleep. This condition was named by Severinghaus and Mitchell after the 1939 play titled *Ondine*, in which a knight, Hans, is unfaithful to a sea nymph, Ondine. In a jealous rage, Ondine places a curse on Hans whereby he must pay constant attention to his breathing!!
- **Heliox**, a low-density mixture of oxygen and helium has been used for treating **asthma** in children by reducing the work of breathing; here, **helium replaces nitrogen** as the inert carrier gas that is mixed with oxygen.
- **Postoperative shivering** is an unpleasant side effect of recovery from anesthesia. **Meperidine (pethidine)** is the drug of choice; other drugs used are clonidine, ketanserin, and doxapram have been used in treatment.
- **Conscious sedation** is sedation with ability to respond to command (used for dental procedures).
- Significant **rise in IOP** occurs during **intubation and laryngoscopy**.
- **Aminoglycoside:** Associated neuromuscular blockade is a rare but potentially fatal adverse event.
- Main route of heat loss causing **hypothermia during anesthesia** is by **radiation**; hypothermia may benefit the patient by providing organ protection against ischemia.
- The **pneumotachograph** is a device for performing **spirometry**; it can also detect dynamic tidal volumes. Different types of pneumotachographs include: *Fleisch, Lily, Venturi Hotwire, turbine, vortex and ultrasound*.
- A **decrease in FRC (functional residual capacity)** of 15–20% occurs on induction of anesthesia.
- **Minimum total air changes** in the **operation theater** should be **20** based on international guidelines.
- During surgical operations and preparation of surgical trolleys, the concentration of airborne particles contaminated by **microorganisms** in the **operating theater** averaged over a five-minute period should not exceed $180/m^3$.

CHAPTER

30

Radiodiagnosis

X-RAYS**Production of X-rays**

- **Roentgen** discovered X-rays in **1895** at the University of Würzburg in Germany; first radiograph was **his wife's hand!**
- The **fundamental difference between X-rays and light rays** is their range of **wavelengths**, **wavelength of X-rays being shorter** than that of visible light. The science of radiology is based on this difference, since substances that are opaque to light are penetrated by X-rays.
- X-rays are produced when **high-speed electrons decelerate rapidly** in a vacuum tube device called the X-ray tube. The tube contains a **tungsten filament (cathode)** and a **metal target (the anode)**, also usually made of tungsten.
- The **X-ray tube is covered by lead** on all sides to absorb emitted X-rays, except for a small exit port.

**Fig. 30.1:** Wilhelm Roentgen

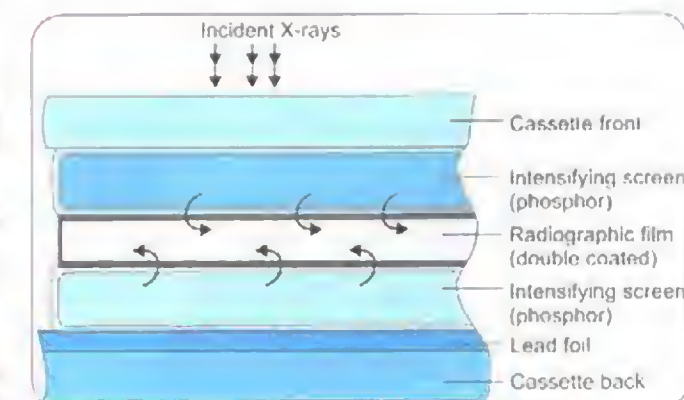
- **Peak kilovoltage (kVp)** is the maximum voltage applied across an X-ray tube; it determines the '**contrast**' of an X-ray image.
- **Scatter:** refers to X-rays that are scattered by tissue but still strike the image receptor; this increases image

noise; scattered radiation reduces image contrast; Noise does NOT convey useful information.

- **Grid:** A grid **controls scatter**. A grid consists of a large number of parallel **lead strips** held apart by material that allows the primary beam of radiation to pass unimpeded, the obliquely scattered radiation being absorbed by the lead strips in the grid.
- **Lead aprons** protect the technicians from the X-ray exposure.
- Dark areas on any X-ray that you see are due to **metallic silver**.

Radiographic Cassette

- Radiographic cassette shown above contains **one sheet** of radiographic **film** sandwiched between two intensifying **screens**.
 - The **screens** consist of polyester plastic coated with **phosphor** layer.
- The **film** consists of polyester plastic coated on **both sides** with photosensitive emulsion of **silver halide (bromide or iodide)** and gelatin.
- When X-rays strike the screens, the screens emit a light flash (fluoresce) - this causes the X-ray film to get 'exposed'.
- The curved arrows in the figure represent light flashes that are created when X-rays strike the screens.
- Note the **lead foil** in the back of the cassette that is designed to stop any X-rays that have penetrated the full thickness of the cassette.



Safelights in X-ray Room

- **Safelights** are *special light fixtures (deep cherry-red color)* fitted with filters used in the *X-ray darkroom* so that it will not affect the *X-ray films and photographic paper*.
- **GBX filters** should be used in the darkroom.
- A **radiographic film** can be left for **40 seconds** in the safelight **without getting fogged**.
- A **distance of 4 feet** should be maintained between the safe light and the processing tray.
- **Wattage of safelight** should be between **7 and 15 W**.
- Inside of darkroom should be painted with *light color* to ensure that safelight is reflected throughout the room.



Fig. 30.2: Safelight, used in X-ray darkrooms

Fluoroscopy

- Fluoroscopy is **realtime radiography**. It allows continuous viewing of a time-varying X-ray image and permit live visual examination of **dynamic events**.
- **Hilar dance sign**—ASD
- **Interrupted bronchus sign**: Bronchial foreign body in main bronchus in children.

ULTRASONOGRAPHY

- **John Wild**: Father of **medical ultrasound**.
- **Ian Donald**: Father of **obstetric ultrasound**.
- Very **high frequency sound (>30,000 Hz)** is used, **transducer** contains **piezoelectric crystals** (*thicker crystals have lower resonance frequency*). MC used synthetic piezoelectric material is **lead zirconate titanate**.
- As the **sound travels through the body** (at **1540 m/s**), it is reflected by tissue interfaces to produce echoes which are picked up by the same transducer and converted into electrical signal.

- Since air, bone and **heavily calcified materials absorb nearly all the ultrasound beam**, ultrasound has **very little use** in the diagnosis of lung or bone disease, but is helpful in detecting and localizing **pleural effusion**.
- **Acoustic impedance** is the **product of velocity and density**.
- **Fluid is a good conductor of sound**; hence, **ultrasound is useful in diagnosing cysts and fluid-filled structures**, which produce large echoes from their walls, but no echoes from the fluid contained within them.
- **Harmonic imaging** is an **ultrasonography technique** that provides **images of better quality** as compared with conventional ultrasound.
- **Ultrasound of the hip** is useful **ONLY upto 6 months of age** due to **ossification of femoral head**.

Ultrasonography is the investigation of choice for

- Gallstones
- Ascites
- Pregnancy monitoring
- To determine spleen and thyroid size accurately
- To distinguish solid and cystic lesions
- For locating non-metallic foreign bodies
- For detecting muscle hernias

Doppler Ultrasonography

- Sound reflected from a mobile structure shows a variable frequency that corresponds to the speed of movement of the structure. The difference in frequency between the sound transmitted and received is known as the **Doppler frequency shift**.
- **Doppler angle**: Angle between the vessel and the transmitted soundwave.
- In color Doppler imaging, the **different colors indicate the direction of bloodflow**:
 - **Red toward** transducer
 - **Blue away** from the transducer
 - **GREEN** indicates turbulent flow. (**Red Tower Blows Away!**).
- Shades (**intensity of color**) represent **velocity of flow**.

Uses of Doppler

- Investigation of choice to detect **venous thrombosis, arterial stenosis and occlusion**, particularly in **carotid arteries** and carotid bruit.
- To assess **blood flow through the umbilical artery**; also estimate **tumor blood flow**.

Echocardiography

- **Two-dimensional Sector Scanning (2D ECHO)**: This demonstrates a fan-shaped slice of the heart in motion.
- Doppler echocardiography measures the **velocity of blood flow**, across valves, within cardiac chambers, and through the great vessels (using ultrasound reflecting off moving red blood cells).
- With Doppler ECHO, it is possible to demonstrate **regurgitation through incompetent valves**; calculate **pressure gradients across the valves** (*modified Bernoulli equation*) and **cardiac output**.
- **2D ECHO** is the **imaging modality of choice** for:
 - Detecting **pericardial effusion**.
 - Diagnosis of **hypertrophic cardiomyopathy**.
 - For imaging valve morphology and motion, including mitral stenosis.

TransEsophageal ECHO (TEE)

- TEE provides **high-resolution imaging of posterior structures of the heart**, particularly the **left atrium, mitral valve, and aorta**.
- TEE with color Doppler is the **test of choice** to detect **perivalvular abscesses**.

Ultrasound Frequencies used in Medicine

- **Higher frequency = Higher resolution BUT lower penetration**; hence, very high frequencies used for eye and **intravascular studies**.
- **Lower frequency = Lower resolution BUT deeper penetration**; hence, used for **abdominal organs**.

Type of Ultrasound	Frequency
TransThoracic ECHO (TTE)	2–3 MHz
Obstetric, abdominal	3–5 MHz
TransEsophageal ECHO (TEE)	5–7.5 MHz
Transvaginal, Transrectal	5–10 MHz
Ocular B scan	10 MHz
Breast	15 MHz
Intravascular U/S	30–40 MHz
Ocular ultrasound biomicroscopy	35–50 MHz

FAST

- **FAST = Focused Assessment with Sonography for Trauma** (**Focused Abdominal Sonar for Trauma**) examines four areas for free fluid/blood in the abdomen.

- Perihepatic space and hepatorenal space (Morrison's pouch) - (Right hypochondrium)
- Perisplenic (left lower chest)
- Pelvis (suprapubic window or Douglas pouch) (hypogastrium)
- Pericardium (epigastrium)
- Limitation of FAST
 - It will **NOT** reliably detect **less than 100 ml** of free blood.
 - It **does not identify injury to hollow viscous**.
 - It **cannot reliably exclude injury** in penetrating trauma.
- **eFAST = Extended FAST = FAST + U/S of bilateral hemithoraces** for finding **pneumothorax and hemothorax**.
- FAST and eFAST mainly used in **blunt trauma**.

eFAST signs suggestive of Pneumothorax on M-mode:

- **'Stratosphere' sign** (aka Barcode sign)
- **'Absence of pleural sliding'** sign
- **'Lung point' sign**
- Absence of comet-tail artefacts and B-lines
- Presence of A-lines
- NOTE: **Seashore (sliding) sign suggests normal lung**

Artefacts in Ultrasound

- **Reverberation artefact**: Caused by the reflection of ultrasound several times back and forth between two closely spaced interfaces. Due to its appearance, the artefact is also referred to as **'ring-down artefact'** (used to detect **free intraperitoneal gas**) and **'comet tail artefact'** (MC used with **cholesterol crystals in the GB, adenomyomatosis or polyps**).
- **'Acoustic enhancement'**: More echoes are received from the tissues behind the cyst.
- **'Acoustic shadow'**: With a **calcified structure**, e.g. **gallstone/calculus**, there is a great reduction in the sound that will pass through, so a **band of reduced echoes** is seen behind the stone.
- **Refraction artifact**: In clinical imaging, this artifact may be recognized in **pelvic structures deep to the junction of the rectus muscles and midline fat**.
- **Beam width and side lobe artefacts**.
- **Mirror image artefact**.
- **Speed displacement artefact**: Seen when the U/S beam encounters an area of **focal fat**.

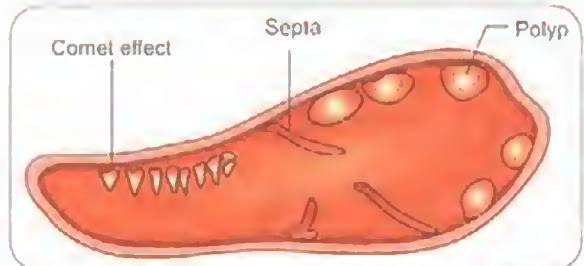


Fig. 30.3: Adenomyomatosis. Small stones in the gallbladder wall cause the comet effect diagnostic of adenomyomatosis. Septa maybe seen. Small polyps are common



Fig. 30.4: US scan shows cholesterosis with adenomyomatosis of gallbladder

CT SCAN (COMPUTED TOMOGRAPHY)

- Tomography refers to the imaging by sections through the use of any kind of penetrating wave (tomography in Greek = 'slice sectioning')
- CT was invented in 1972 by **Godfrey Hounsfield** of England (Nobel prize winner), and independently by South African born physicist **Allan Cormack** of Massachusetts.
- The computer calculates the attenuation (absorption) value of each picture element (known in computer language as a 'pixel'). Each *pixel* is 0.25-0.6 mm in diameter.
- The **attenuation value** is expressed in **Hounsfield units** and values are shown here.

Bone	+ 1000 U
Water	0 U
Air	- 1000 U

'BeWAre'

- Also know **HU** of lung = - 700; fat = - 50; CSF = +15; Blood = +30-45; Muscle = +40;
- Wall, door, floor, ceiling of **CT scan room** should be coated with 1/16 inch thick **lead** (this is equivalent to 4-6 inches thick concrete wall!).
- CT is very **useful** for scanning **adrenals, pancreas** and **mediastinum**.
- Non, ionic contrast agents (**iodine-based**) described under contrast agents section may be used.

Newer CT scanners

- **Spiral CT**
 - Aka **helical CT or multidetector CT (MDCT)**: Here the X-ray tube **continuously rotates** around the patient in a **spiral manner** as the patient holds his or her breath and acquires data. The spiral CT machine **does not** need to reset itself after each image is taken thus **eliminating the problem of misregistration**.
 - **Advantages**: Shorter scan times (**entire body** can be scanned in **30 seconds**!), reduced patient and organ motion, CT angiograms can be done.
- **HRCT (High resolution CT)**
 - **Narrow slice width** is used and **thin sections** are obtained (**1-2 mm**) and reconstructed using a sharp **algorithm** (e.g. **bone algorithm**);
 - Investigation of choice **detecting early interstitial lung disease**;
 - Investigation of choice for **bronchiectasis**;
 - NOT suitable for lung cancers and mediastinal imaging;
 - NO contrast is used.



Fig. 30. 5: Godfrey Hounsfield

MAGNETIC RESONANCE IMAGING

- Magnetic resonance imaging (MRI) was invented by **Lauterbur** in 1973.
- Magnetic resonance imaging depends on the **rearrangement of hydrogen nuclei (protons)** in water molecule and lipids when a tissue is **exposed to a short electromagnetic pulse**.
- When the pulse subsides, the nuclei return to their normal position, re-radiating some of the energy they have absorbed. Sensitive receivers pick up this electromagnetic echo.
- **Clinical MRI machines operate between 0.5 and 3.0 tesla**.
- **MRI rooms** are shielded completely by a continuous sheet or wire mesh of copper or aluminum to shield the imager from external electromagnetic radiations called **Faraday cage**.



Fig. 30.6: Paul Lauterbur

T1 and T2 Images

- In MRI, the rate of return to equilibrium of perturbed protons is called the **relaxation rate**. The relaxation rate varies among normal and pathologic tissues.
- Two relaxation rates, T1 and T2, influence the signal intensity of the image.
- The T1 and T2 signals are analyzed by the computer and reconstructed mathematically by a method called **Fourier transformation**.
- **T1 relaxation time** is the time, measured in milliseconds, for 63% of the hydrogen protons to return to their normal equilibrium state.
- **T2 relaxation** is the time for 63% of the protons to become dephased owing to interactions among nearby protons.

- Various body tissues have different relaxation times so that a given tissue may be **T1 weighted or T2 weighted** (i.e. best visualized on that particular type of image). In practice, both types of scans are usually performed.
- **Paramagnetic substances** like **Fe, Mg and Gadolinium** cause a **decrease in T1 and T2 times** (i.e. they increase the rate of relaxation of T1 and T2.).

	T1-weighted images	T2-weighted images
Best for	Normal anatomy, subacute hemorrhage	Viewing pathological changes, chronic hemorrhage
Hypointense (dark/black) structures	CSF, vitreous, edema	Blood vessels
Hyperintense (Bright/white) structures	Fat, blood and contrast agents	Water, CSF, vitreous, edema, Inflammation, IV disk (all have high water content), 'WaTer is white on T2'

Enhancement in MRI

- **Gadolinium** is a **non-iodine contrast agent** given **IV**, remains intravascular unless there is a breakdown of the BBB. It is **only visualized on T1-weighted images** and **enhancing lesion, such as tumors and inflammation will appear bright on these images**. It **DOES NOT** show up on T2, weighted studies.
- In children < 2 years **bone marrow** enhances intensely with contrast, whereas **adult marrow** does NOT enhance.
- As a general rule, **the normal marrow (red or yellow marrow) in adult is hyperintense on T1W MR image**.
- **Fat suppression techniques**: Eliminate the brighter signal of fat and better delineates normal structures as well as tumors, inflammatory lesions and vascular malformations, e.g. T1 fat saturation with gadolinium; **STIR** (short T1 inversion recovery, **best for optic neuritis**).
- **FLAIR (Fluid Attenuation Inversion Recovery)** suppress the bright CSF on T2-weighted images to allow better visualization of adjacent pathological tissue, such as **periventricular plaques of demyelination**; FLAIR is more sensitive for **edema**.

Advantages of MRI

- **NO ionising radiation**; images can be easily produced in any plane, e.g. sagittal and coronal (good for spinal cord, aorta, vena cava)
- Note: Radiation exposure in CT > Bone Scan > X-rays (max to min).

- Visualization of posterior fossa and other areas prone to hony artefact on CT is better (e.g. craniocervical junction).
- Shows vasculature without contrast
- High inherent soft-tissue contrast, precise staging of malignancy possible

Contraindications to MRI

- Patients with metallic FB, e.g. pacemakers, cochlear implants, some types of aneurysm clips, metallic intraocular foreign body
- McGee stapedectomy piston prosthesis
- Duraphase penile implant
- Swan-Ganz catheter
- Magnetic stoma plugs, Magnetic dental implants, magnetic splinters
- Tattooed eyeliner (contains ferromagnetic material and may irritate eyes)
- Ferromagnetic IVC filters, coils, stents (safe 6 weeks after implantation).

Disadvantages of MRI

- High cost; **Claustrophobic**; motion artifacts due to longer imaging time; **nephrogenic systemic fibrosis** (in renal insufficiency patients due to gadolinium).
- Does **NOT image bone/calcification** (which appears black); although not always a disadvantage since bone marrow can be visualized (e.g. tumors extension into bone marrow).
- Does NOT detect acute hemorrhage.

Different Types of MRI

- Echo-Planar MRI (EPI): **Extremely rapid MRI of the brain in 1-2 mins.** Perfusion and diffusion imaging are EPI techniques that are useful in early detection of ischemic injury of the brain and may be useful together to demonstrate infarcted tissue as well as ischemic but potentially viable tissue at risk of infarction (e.g. the **ischemic penumbra**).
- **Diffusion weighted MRI:** Is the **most sensitive technique for detection of acute cerebral infarction at <7 days' duration.**
- **Perfusion MRI** involves the acquisition of EPI images during a rapid intravenous bolus of gadolinium contrast material. It can also be used in the **assessment of brain tumors** to differentiate intra-axial primary tumors from extra-axial tumors or metastasis.
- **Diffusion tensor imaging** is a diffusion MRI technique that has great potential in the **assessment of brain maturation**; valuable in **preoperative assessment of subcortical white matter tract anatomy prior to brain tumor surgery.**
- **Functional MRI** of the brain is an EPI technique that **localizes regions of activity in the brain** following task activation; useful in research. Currently **preoperative somatosensory and auditory cortex localization** is possible.

- **Magnetic Resonance Neurography** is a T2-weighted MR technique that shows promise in detecting increased signal in irritated, inflamed, or infiltrated peripheral nerves.
- **Time-of-flight (TOF) imaging,** MC used method for MR angiogram (MRA).
- 'When any motion of body produces disturbance and motion related artifact in images in **radiology or during radiotherapy**, then **gating** is done to **reduce the motion-related artifacts (such as during breathing)**'.
- **MRCP** (magnetic resonance cholangiopancreatography) is a noninvasive technique for visualizing biliary and pancreatic ductal system; MRCP uses **heavily T2- weighted** sequences that depict **biliary and pancreatic ducts** as high intensity structures; **3D MRCP** allows a multiplanar reconstruction with **MIP** (maximum intensity projection) algorithm.

MRI is BEST for	CT scan is BEST for
CNS <ul style="list-style-type: none">• Intracranial space occupying lesions (IC SOL) (esp. posterior fossa tumors)• Acoustic neuroma/ vestibular schwannoma• Acute ischemic stroke (diffusion-weighted MRI)• CNS vascular malformation• Demyelinating disease (multiple sclerosis)• Cranial neuropathy (MRI with contrast)• Brain abscess, epidural abscess• Meningeal disease (MRI with contrast)	<ul style="list-style-type: none">• Acute subarachnoid hemorrhage (noncontrast CT)• Acute hemorrhagic stroke (noncontrast CT)• Fractures of cervical spine• Pulmonary embolism (CT angiography)• Bronchiectasis (HRCT)• Hypersensitivity pneumonitis (HRCT)• Acute aortic dissection (esp for emergency patients; MRI for stable patients)• Chronic sinusitis• Juvenile nasopharyngeal angiofibroma
Spine <ul style="list-style-type: none">• Spinal cord compression• Prolapsed IV disk• Post LP headache (for site of leak)	<ul style="list-style-type: none">• Thyroid-associated ophthalmopathy• Pancreatic cancer (spiral CT)• Esophageal perforation• Adrenal gland lesions
Others <ul style="list-style-type: none">• Entrapment neuropathies• Right ventricular dysplasia• Chronic aortic dissection	

POSITRON EMISSION TOMOGRAPHY

Positron Emission Tomography (PET)

- An imaging technique which produces a 3D image of **functional/physiological processes** in the body. The system detects pairs of gamma rays emitted indirectly by a **positron-emitting radionuclide (tracer,**

MC **fluorodeoxyglucose (18-FDG or F-18)**, which is introduced into the body on a **biologically active molecule.** Images of tracer concentration in 3-D space within the body are then reconstructed by computer analysis.

- A **cyclotron** is required to create the necessary isotopes, and, therefore, PET is currently restricted to large research centers; PET and CT scan together in one machine is latest.
- **Positron emitters** (used in PET): Oxygen-15; Carbon-11; Nitrogen-13; Fluorine-18
- **Uses of FDG PET scan:**
 - Detection of **extra-organ metastases** or **occult metastases.**
 - Differentiating **benign and malignant pleural disease**
 - In **Alzheimer's disease:** a **lower activity of FDG** in **parietal lobes** has been reported.

Single photon emission computed tomography (SPECT)

- It is a nuclear medicine imaging technique using gamma camera to image the injected radio-isotope.
- Used for functional imaging of cerebral and cardiac perfusion.
- In SPECT, because only a single photon is emitted from the radionuclides used for SPECT, a special lens known as a **collimator** is used to acquire the image data from multiple views around the body. The use of a collimator results in a **tremendous decrease in detection efficiency** as compared to PET.

Radiation Exposure

Source of Exposure	Radiation Dose
Dental X-ray	0.005 mSv
Chest X-ray	0.02 mSv
CT scan head	2-3 mSv
CT scan chest	8 mSv
Whole body CT scan	10 mSv
Abdomen and pelvis CT	8-11 mSv
PET-CT	5-15 mSv
SPECT	2-5 mSv

Key: mSv – millisieverts

EXTRA EDGE

- **CT scan of abdomen and pelvis** has a radiation dose equivalent to approximately **500 chest X-rays.**

OLDER TECHNIQUES

- **Infrared thermography:** Measures body heat that is constantly radiating away from the surface of the skin. Thermography's best use is its inherent ability to detect subtle, vascular and physiological changes in blood flow. Was earlier popularized for cancer detection – not proven.
- **Myelography:** Involves the intrathecal instillation of specially formulated water-soluble iodinated contrast medium into the lumbar or cervical subarachnoid space. It has been largely replaced by CT myelography and MRI. In **intradural extramedullary spinal tumor, expansion of subarachnoid space** on the ipsilateral side producing a meniscus and displacement of cord to contralateral side is seen.

Newer techniques

- **Magneto-encephalography (MEG)**
 - It is an imaging technique used to **measure the magnetic fields produced by electrical activity in the brain** via extremely sensitive devices known as **SQUIDS.**
 - Uses for the MEG, include **assisting surgeons in localizing a pathology, assisting researchers in determining the function of various parts of the brain, neurofeedback,** and others.
- **Near infrared spectroscopy (NIRS)**
 - It is an **optical technique for measuring blood oxygenation in the brain;** indirect measure of brain activity.
 - NIRS is also used to measure cerebral blood flow in **perinatal asphyxia.**

CONTRAST MEDIA

Negative contrast media	Positive contrast media
<ul style="list-style-type: none">• Low atomic number• Radiolucent (do not readily absorb radiation) – show on the radiograph as dark area• Can be used with positive contrast agents to provide double contrast, which often provides the best mucosal detail• For examples: CO₂, oxygen and air	<ul style="list-style-type: none">• High atomic number• Radio-opaque (readily absorb radiation) – show on radiograph as a light area• For examples: Barium and iodine compounds

Barium Sulphate Preparations

- Used for investigation of **alimentary tract;** It is completely insoluble and is therefore neither acted on by the alimentary secretions nor absorbed through the intestine.

- **Barium sulfate**, usually prepared in a fine colloidal suspension, provides excellent detail of the mucosal pattern (*barium carbonate is extremely poisonous*).
- **Enteroclysis** = Contrast study of small bowel fluoroscopically; double contrast with barium (coats bowel wall) and methylcellulose (distends small bowel)

Iodinated Contrast Agents

- Since the soluble salts of barium are poisonous, insoluble barium sulphate is used **only** as an oral suspension (Barium 137).
- **Intravascular** contrast agents are primarily **iodine based**.
- An indication of the osmolality of the agent is given by the **iodine-to-particle ratio (contrast agent ratio)**.
- **Non-ionic dimers** have the **highest ratio of 6:1**.
- **Non-ionic dimers** are also **iso-osmolar with plasma** (300 mosm/kg).

Classification of Iodinated water soluble contrast agents

- **High Osmolar Ionic Monomers:** amidotrizoate (detrizoate); iothalamate; ioxithalamate; metrizoate.
- **Low Osmolar Ionic Dimers:** ioxaglate.
- **Low Osmolar Non-ionic Monomers:** iobitridol; iopentol; iohexol; iomeprol; iopamidol; iopromide; ioversol; ioxilan.
- **Iso-osmolar Non-ionic Dimer:** iodixanol; iotrolan.
- Uses of iodinated contrast media
 - **For angiography:** Low osmolar non-ionic monomers are the agents of **choice** (safer than high osmolar).
 - **For CT scans** requiring contrast and CT angiography.
 - For **hysterosalpingography** and rarer procedures such as **myelography**, **oral cholecystography** (Graham Cole test) also, low osmolar non-ionic monomers are the agents of **choice**.
 - Can also be used to outline bile ducts and pancreatic ducts in ERCP.
 - Diluted water soluble iodinated contrast agents can be used for arthrography, ductography, bronchography and lymphography.
- Advantages of Nonionic Over Ionic Contrast Agents
 - **Non ionic agents:** **Reduced tonicity** (nearly isotonic) - implies reduced adverse reaction.; **lower neurotoxicity** (can be used for myelography); **lower chemical toxicity** (increased hydrophilia = fewer tendencies to cross cell membranes); **decreased hypersensitivity** reactions.
 - **High osmolar ionic agents:** are a/w erythrocyte damage, endothelial damage, vasodilation, hyperr-

plenia, interruption of blood brain barrier, and cardiac depression.

EXTRA EDGE

- **Gastrografin** (sodium + meglumine amidotrizoate): A high osmolar water soluble agent suitable only for oral/rectal administration.
- **Lipiodol:** Oil based iodinated contrast to outline ducts of lacrimal and salivary glands.

Contrast Nephropathy

- Occurs due to **direct renal tubular epithelial cell toxicity** and **renal medullary ischemia**.
- Defined as an **increase in creatinine >0.5 mg/dL or 25% above baseline** that occurs 48-72 hours after contrast administration.
- Serum creatinine begins to rise in **48-72 hours**; it peaks in **3-5 days** and returns to normal by **10-14 days**.
- **Nonionic contrast media** may be **less toxic**.
- Treatment: **Pretreat** with one liter of IV 0.9% (normal) saline over 10-12 hours **both before and after the contrast administration**; pretreatment with **N-acetylcysteine** also decreases the risk.

Predisposing factors for contrast nephropathy

- Advanced age, Anemia, ACE inhibitors
- Congestive heart failure
- Diabetic nephropathy (also preexisting kidney disease)
- Multiple myeloma
- **Metformin** (**lactic acidosis risk**; STOP 48 hrs before procedure)
- **NSAIDs**

EXTRA EDGE

- Serum creatinine <1.5 mg/dL is normal; > 2mg/dL is a **contraindication** for IV contrast.
- Because the use of **CO₂** is not a/w nephrotoxicity or allergic reactions, it is increasingly being used as a contrast agent for **ortography** as well as for outflow assessment, renal arteriography, and visceral angiography.
- **Prapylotic** administration of **corticosteroids** is recommended in **high-risk patients** receiving contrast (bronchial asthma, previous allergic reaction, etc.).

Nephrogenic Systemic Fibrosis

- Aka **nephrogenic fibrosing dermopathy**.
- A/w **gadolinium** contrast use in CKD (chronic kidney disease) patients.
- Seen primarily with a **GFR < 15 mL/min/1.73 m²**, but rarely with a **GFR of < 30 mL/min/1.73 m²**.
- There is an **increase in dermal spindle cells** positive for **CD34 and procollagen I**.

- **Multisystem** disorder; MC is a debilitating fibrosing skin disorder - **skin can be thick and woody** in areas and is **painful out-of-proportion** to findings on examination.

EXTRA EDGE

- Acute **compartment syndrome** of the forearm, resulting from **contrast dye extravasation** presents as **upper extremity ischemia**; a/w **contrast enhanced CT** (less common in MRI due to lower quantity of contrast used); treat with immediate **fasciotomy**.

Embolization Agents

Embolizing agents are used in interventional radiology for occluding AV malformations or tumor blood vessels as in shown here:

Solid agents	Liquid agents
Polyvinyl alcohol particles	Pure ethanol (absolute alcohol)
Gelfoam	Cyanoacrylate
Balloons	Onyx
Coils	Polyvinyl acetate
Microfibrillar collagen	Cellulose acetate polymer
Microspheres (starch, etc.)	Hypertonic glucose
Silk sutures	Barium sulfate
Thrombin	Silicone
	Hot contrast agents
	Sclerosing agents (sodium tetradecyl sulfate, sodium morrhuate, polidocanol)

Radiological Investigations of Choice

- **Renal artery stenosis:** Renal angiography
- **Mesenteric arterial occlusion:** Mesenteric angiography
- **Cholelithiasis** (bile duct stones): ERCP
- **Colonic mucosal disease:** Colonoscopy (better than barium enema)
- **Primary sclerosing cholangitis:** Magnetic resonance cholangiopancreatography (MRCP)
- **Chronic pancreatitis:** MRCP
- **Neuroendocrine tumors:** Somatostatin receptor scintigraphy
- **UGIB** (upper GI bleeding): Upper GI endoscopy
- **LGIB** (lower GI bleeding): Colonoscopy
- **Proximal DVT:** Venous ultrasonography
- **Duplex ultrasonography** for detecting and grading the degree of stenosis at the carotid bifurcation.

SKELETAL SYSTEM/BONES

Bone Metastases

Osteoblastic metastases	Osteolytic metastases
<ul style="list-style-type: none"> • Overall, lytic mets are more common • Prostate (mainly blastic; MC cause of blastic mets) • Carcinoid • Lymphoma 	<ul style="list-style-type: none"> • Thyroid • Kidney • Lung • Breast (mainly lytic but rarely blastic) • Multiple myeloma

Ankylosing Spondylitis

- **Earliest change** is haziness of sacroiliac joint (**sacroilitis**).
- **Enthesopathy:** Calcification at the attachments of the muscles, tendons and ligaments particularly around the pelvis and heel.
- **Shiny corner sign (Romanus lesion)** is an early spinal finding; these represent small erosions at the superior and inferior endplates (corners on lateral radiograph) of the vertebral bodies, with surrounding reactive sclerosis.
- **Squaring of vertebrae**
- **Bamboo spine** appearance.
- **Andersson lesion** is a discovertebral fracture seen in ankylosing spondylitis.
- **Dagger sign:** A single central radiodense line on frontal radiographs related to ossification of supraspinous and interspinous ligaments.
- **Trolley/Tram track sign:** Three vertical linear increased density lines.



Figs 30.7A and B: AP view showing dagger and trolley track sign and lateral view showing classical bamboo spine in ankylosing spondylitis

Rickets

- Relative or absolute deficiency of vitamin D; presents by 3–6 months, almost always < 2 years; increased uncalcified osteoid in the immature skeleton.
- Changes at the growth plate
 - **Fraying, splaying and cupping of metaphysis** (distal ends of radius and ulna) = **earliest change**
 - **Widened growth plate**
 - **Epiphyseal separation** is MC in **renal rickets**
 - **Rachitic rosary** = cupping of anterior ends of ribs, and, on palpation, abnormally large costochondral junctions
 - **Looser's zones** *uncommon* in children
 - On treatment, **Muller's lines** in the widened space at the site of zone of preparatory calcification are the first sign of healing.
- Changes due to bone softening (deformities)
 - **Bowing** of long bones
 - **Triradiate pelvis**
 - **Harrison's sulcus** = indrawing of the lower part of the chestwall because of soft ribs
 - Scoliosis, biconcave vertebral bodies, basilar invagination
 - **Craniotabes** = flattening of the occiput and accumulating osteoid in the frontal and parietal regions.
- General changes
 - ↓ bone density = uncommon
 - Retarded bone maturation and growth
- Earliest signs of healing** in rickets is provided by radiological examination; Thacher's scoring is used.



Fig. 30.8: Marked anterior bowing of tibia and fibula is seen in rickets with increase in distance between the epiphyses and metaphyses (*widened physes*)

Scurvy

- Occurs due to *vitamin C* deficiency
- Onset at 6 months to 2 years; rare in adults. **Earliest signs** are seen at the **knees**.
- Wimberger's line/ring**: Sclerotic ring around epiphysis indicating loss of epiphyseal density.
- Dense zone of provisional calcification** due to excessive calcification of osteoid. ↑ density at the ends of long bones seen as '**white line of Frenkel**'.
- Zone of rarefaction proximal to white line—**Trummerfeld zone** – metaphyseal lucency.
- Pelkan spur**: Metaphyseal corner fractures through the weakened lucent metaphysis.
- Ground glass appearance of shaft of diaphysis.
- Thin cortex (**pencil point cortex**)
- Periosteal reaction due to **subperiosteal hematoma**.
- Osteoporosis (usually the *only sign seen in adults*).



Fig. 30.9: Scurvy. X-ray wrist AP view reveals increased density of the zone of provisional calcification (Frankel's line) with a lucent zone beneath it (Trummerfeld zone) in the distal radial and ulnar metaphysis

Osteomalacia

- Looser's zones** (*pseudofractures*) – radiolucent band of few millimeters, usually perpendicular to the surface of the bone; usually at the inner aspect of neck of femur, pubic ramus, axillary border of scapula and ribs; these are caused by rapid resorption and slow mineralization and may be surrounded by a collar of callus.
- Protrusio acetabuli**—acetabulum protruding into pelvis.
- Triradiate pelvis** in females.
- Bone biopsy** from the iliac crest *confirms the diagnosis*.
- Characteristic histological finding is **excessive uncalcified osteoid**.



Fig. 30.10: Looser's zones in inner margins of proximal femur (white arrows) and the superior and inferior pubic rami in osteomalacia

Psoriatic Arthritis

- Occurs in almost **30% patients** with psoriasis.
- NO juxta-articular osteoporosis, i.e. *preserved bone density* (unlike RA).
- Periosteal new bone particularly in the hands and feet.
- Asymmetrical destruction of **distal interphalangeal (DIP) joint** with ankylosis.
- Resorption of terminal tufts with '**pencil in cup**' deformity; **Ivory phalanx**.
- 'Opera glass hand'** (*main en lignette*—telescoping of one bone into its neighbor).
- Destruction of **first toe interphalangeal joint** with periosteal reaction and bony proliferation at distal phalangeal base (*pathognomonic*).
- Asymmetrical syndesmophytes (lower cervical to upper lumbar spine).
- Squaring of vertebrae in lumbar spine; paravertebral soft-tissue calcifications.
- Bilateral asymmetrical sacroilitis; a/w **HLA B-27 antigen**, negative rheumatoid factor.

Delayed skeletal maturation	Accelerated skeletal maturation
<ul style="list-style-type: none"> Chromosome disorders; Trisomy 21, trisomy 18. Endocrine disorders: Hypothyroidism, Cushing's disease and steroid therapy, hypogonadism, hypopituitarism. 	<ul style="list-style-type: none"> Constitutional disorders: McCune-Albright syndrome (polyostotic fibrous dysplasia with precocious puberty), cerebral gigantism (Sotos syndrome), lipodystrophy, pseudohypoparathyroidism, acrodysostosis, Weaver-Smith syndrome, Marshall-Smith syndrome.

Contd...

Contd...

Delayed skeletal maturation	Accelerated skeletal maturation
<ul style="list-style-type: none"> Chronic illness: Congenital heart disease (particularly cyanotic), renal failure, inflammatory bowel disease, malnutrition, rickets, and maternal deprivation. Others: Most bone dysplasias, malformation syndromes. 	<ul style="list-style-type: none"> Endocrine disorders: Idiopathic sexual precocity, adrenal and gonadal tumors, hyperthyroidism, intracranial masses in the region of the hypothalamus (hamartoma, optic chiasm glioma, astrocytoma) hydrocephalus and encephalitis. Others: Large or obese children.

Eosinophilic Granuloma

- MC type of **histiocytosis X**.
- Age 5–10 yrs; Presentation: bone pain, local swelling, irritability
- Lungs**: Involved in apical reticulonodular infiltrates, *honeycomb lung*
- Bones**
 - MC solitary/monostotic lesions.
 - **Skull/mandible**: '**Punched-out**' lucencies with *beveled edges* and no surrounding sclerosis (*geographical skull*), '**hole within a hole**'/'**hole in bone**' appearance, '**button sequestrum**', '**floating teeth**' sign.
 - **Spine/pelvis**: **Vertebra plana** with intact intervertebral disks.
 - **Long bones**: medullary lucency +/- thin sclerotic rim.

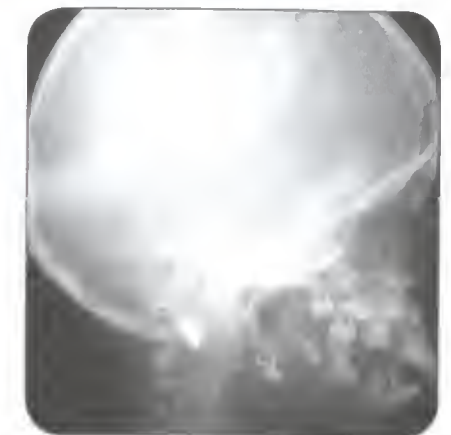


Fig. 30.11: Histiocytosis. Floating teeth appearance

Achondroplasia

- Autosomal dominant (**AD**); MC cause of *short limbed dwarfism*; a/w *increased paternal age*; *normal intelligence*.

- **FGF3** (gain of function) mutation on **chromosome 4p** which causes abnormal cartilage function.
- **Short extremities** (short femur and humerus-**rhizomelic** shortening) and ribs *vs* trunk length.
- **Pelvis**: Squared iliac wings (**tombstone iliac wings**) and narrow sacrosciatic notch (**champagne glass pelvis**).
- **Hands**: Fingers widely opposed and equal length (**trident hands/starfish hands**).
- **Skull**: Enlarged vault and mandible, *small foramen magnum*.
- **Spine**: Narrow AP diameter with concave posterior surface and **narrow spinal canal** only 1/2 normal depth, decreased lumbar interpedicular distance, hypoplastic (**'bullet nose'**) thoracolumbar vertebrae.
- 'Ball-in-socket' epiphyses, widened metaphyses.
- Can be diagnosed before birth by third trimester antenatal ultrasound; AT and after birth conventional X-rays are the investigation of choice.



Fig. 30.12: Square-shaped pelvis (tombstone iliac bones) and short thick bones in achondroplasia

Hyperparathyroidism

- **Subperiosteal resorption** of phalanges (particularly radial side of middle phalanx of middle finger).
- **Loss of lamina dura** of tooth.
- **Brown's tumor** is an expansile **lytic** lesion, which appears like a bone tumor.
- **'Pepper pot'** appearance of the skull.
- **'Rotting fence post'** appearance of proximal femur.
- **Terminal tuft** bony erosion.



Fig. 30.13: Brown tumors—radiograph of left ankle of young man with hyperparathyroidism shows multiple well-defined expansile multiloculated lytic lesions in lower end of tibia and fibula

Sickle Cell Anemia (Bone Findings)

- Deossification due to marrow hyperplasia:
 - ↓ Bone density in skull with widened diploic space (**'Hair-on-end'** or 'hairbrush' appearance)
 - **'H-shaped vertebrae'** or 'fish vertebrae' or 'step-off' vertebra
 - Rib notching
- Thrombosis and infarction
 - **Avascular necrosis**, especially femoral head
 - Periosteal reaction (**'bone within bone'**)
 - Snowcap sign: medullary bone infarct of subarticular area
- Secondary osteomyelitis: more susceptible to *Salmonella* (especially affects sickle cell patients); Dactylitis = **'Hand foot syndrome'**
- Growth effects: Bone shortening secondary to ↓ blood supply.

Hemophilic Arthritis

- **Incidence: knees MC**; results in secondary OA.
- **'Squared' patella** (flattened inferiorly).
- **Widened intercondylar notch, tibiotalar slanting.**
- Subchondral cysts.
- Severe osteopenia.
- Talar tilt
- Premature closure of epiphysis leading to short bone with enlarged end.

Wormian Bones

Small ossicles within cranial suture lines:

- **P**: Pyknodysostosis, progeria
- **O**: Osteogenesis imperfecta
- **R**: Rickets in healing phase
- **K**: Kinky hair syndrome
- **C**: Cleidocranial dysplasia, cretinism
- **H**: Hypothyroidism/hypophosphatasia
- **O**: Otopalatodigital syndrome
- **P**: Primary acro-osteolysis (Hajdu-Cheney)/pachydermoperiostosis
- **S**: Syndrome of Down
- Mnemonic **'PORK CHOPS'**

Bone within Bone Appearance

- Sickle cell disease
- Thorotrast
- Osteopetrosis
- Paget's disease, Postradiation
- Prostaglandin E1 therapy (in infants with patent ductus arteriosus dependent heart disease)
- Acromegaly, Gaucher's disease
- Normal neonate
- Hypervitaminosis **D**
- Heavy metals (bismuth, lead, thorium)
- Mnemonic **'STOPP AND heavy metal'**

Generalized Increased Bone Density

- **Renal** osteodystrophy
- Sickle cell disease
- **Metastasis** (osteoblastic)
- **Osteopetrosis**
- Paget's disease, pyknodysostosis
- **Myelofibrosis**
- **Mastocytosis**
- **Fluorosis**
- **Hyperparathyroidism**; hypervitaminosis A and D
- **Lymphoma**
- Mnemonic **'Regular Sex Makes Old People Much More Fit, Healthy and Lively!'**

SPINE/VERTEBRAE

Vertebrae

- **'Rugger jersey' spine** = osteo**PET**rosis; Renal osteodystrophy (**PETROI**).
- **'Ivory' vertebrae** = Lymphoma (Hodgkin's), Infection, Metastases, Paget's disease; **LIMP**.
- **'Codfish' vertebrae** = Osteoporosis, Osteomalacia, Sickle cell disease; **OOS**.
- **'Bullet-shaped' vertebrae** = Hurler disease, Achondroplasia, Morquio disease; **HAM**.

Intervertebral Disk Calcification

- **Alkaptonuria**
- **CPPD disease**; Gout; Ankylosing spondylitis; **JRA**; **Hemochromatosis**; **Diffuse idiopathic skeletal hyperostosis (DISH)**; **Degenerative spondylosis**; **Following spinal fusion**; **Idiopathic** (transient phenomenon in children), **cervical spine MC affected**.
- Clinically a/w neck pain and fever but may be asymptomatic persistent in adult.

Vertebra Plana (Calve-Kummel-Verneuil Disease, Vertebral Osteochondrosis)

- **Avascular necrosis** of vertebral body; Age: 2-15 years
- Causes: Fracture, Eosinophilic granuloma, Tumor, Infection, Steroids, Hemangioma, (**FETISII**)
- X-ray = Vertebral body becomes flat thin disk, ↑ density of vertebra, neural arches not affected, **disk spaces are normal with normal intervertebral disk space**, intervertebral **'vacuum cleft' sign** (pathognomonic), no kyphosis.



Fig. 30.14: Vertebra plana in a case of histiocytosis (eosinophilic granuloma)

Scoliosis

- **Cobb's angle**: Angle between the line passing through the margins of vertebrae at the ends of the curve.
- **Reisser's sign**: Iliac apophysis fuses with the iliac bone at maturity and indicates the completion of growth, and, thus, no possibility of the curve worsening.

Atlantoaxial Subluxation

- **Arthritic**: **Rheumatoid arthritis**, **JRA**, psoriatic arthritis, ankylosing spondylitis (late feature in 2%)
- **Congenital**: Down syndrome, Morquio syndrome, atlanto-occipital fusion, congenital absence/hypoplasia of dens
- **Others**: Infectious retropharyngeal abscess, traumatic.

Spondylolisthesis

- A forward slip of vertebra **L5 on S1**.
- In a **normal vertebra** (in oblique view of spine), the interpeduncular region gives a '**Scottish dog**' appearance.
- In **spondylolisthesis** (in oblique view of spine), '**Beheaded Scottish dog**' appearance is seen.
- **AP view X-ray is least useful except** in cases of **inverted Napoleon Hat** sign (appearance of the L5 vertebra on an AP X-ray in severe spondylolisthesis).
- MRI shows spinal cord compression, CT scan shows bony slippage.
- ALSO KNOW: **Spondylolysis**—it is a defect in the pars interarticularis of the vertebral arch; if the appearance is of a **Scottish dog wearing a collar**, defect is in the pars interarticularis and the patient has spondylolysis.

Diffuse Idiopathic Skeletal Hyperostosis (DISH)

- Aka Forestier disease
- Characterized by **bone proliferation at sites of tendinous and ligamentous insertion of the spine** affecting **elderly individuals**.
- Florid, **flowing ossification** is noted along the anterior or right anterolateral aspects of at least four contiguous vertebrae; **disk spaces are usually well preserved**
- Maybe a/w **ossification of posterior longitudinal ligament, hyperglycemia and HLA-B27**.

Ossification of Posterior Longitudinal Ligament

- MC involves **cervical spine** causing cervical myelopathy; MC in **men**; MC in **Asians**. ('Asian men are a pain in the neck!!')
- May be a/w **DISH**, ankylosing spondylitis, **schizophrenia!**, ossified ligamentum flavum (yellow ligament).
- **T2-weighted MRI** is best for **diagnosis** and shows **hypointensity**.
- '**Blooming artefact**' on gradient echo MRI can **overestimate the canal stenosis**.

RESPIRATORY SYSTEM

PA and AP Views of Chest Compared

- Erect inspiratory **posteroanterior (PA)** is the **preferred CXR view**. The patient stands in front of a radiographic plate, hands on hips, with the **X-ray source 2 m behind**.
- An anteroposterior (AP) CXR is performed in bed-bound patients unable to stand for a PA view, or those

who require a portable CXR when it is unsafe to move them to the radiology department. The **X-ray cassette is placed behind the patient and the X-ray taken from the front** (Figure 30.15 and 30.16).

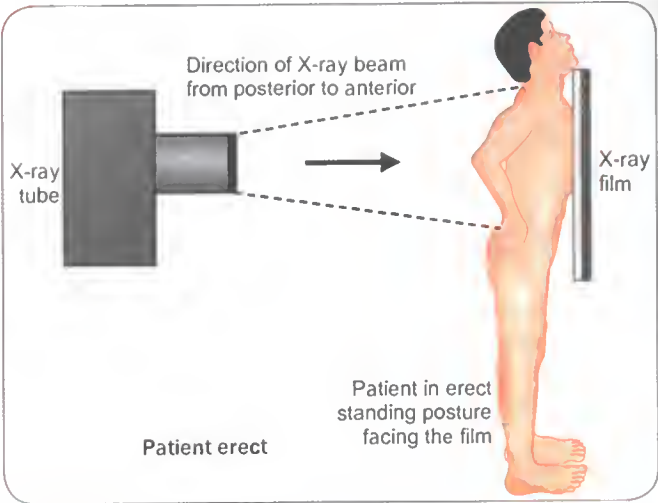


Fig. 30.15: Patient positioning for a typical erect chest X-ray in PA view

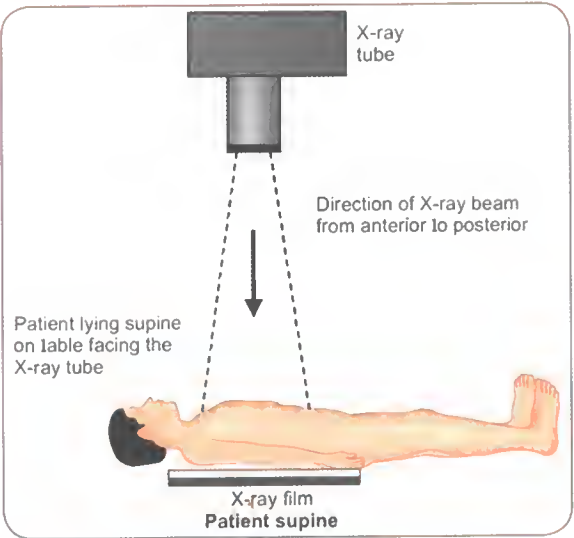


Fig. 30.16: Patient positioning for a typical supine (bed side) chest X-ray in AP view

Structure	PA radiograph	AP radiograph
Heart	Little magnification	Magnified image
Scapulae	Rotated way from lung fields	Superimposed on lung fields
Clavicles	2 inches below apex	Above apex
Rotational artefact	Less	More

Normal CXR—Important Points (Figure 30.17)

- **Trachea:** Should be central, with slight deviation to the right as it crosses the aortic arch; Cervical spinous process seen through tracheal air column.
- **Superior mediastinum:** Should have a width <8 cm on a PA CXR.
- **Cardiothoracic ratio (CTR):** The maximum transverse diameter of the heart should not exceed 50% of the maximum transverse diameter of the chest on a standard PA CXR, i.e. normal CTR = 0.5..
- The left **hilum** is usually higher (2 cm) and squarer than the V-shaped right hilum.

- **Right hemidiaphragm** is usually **higher than the left** by 2.5 cm (because of the liver).
- Both **lung fields should be equally translucent**; in case of **patient rotation**, one side becomes darker than the other.
- Approximately, 90% of the pulmonary vascular structures are appreciated at the mid and lower zones. This is an effect of gravity.
- There should be **no free gas present under the diaphragm**. On the **left side**, a **gastric air bubble** is frequently seen. On the **right side**, **interposid large bowel** may occasionally be seen (Chilaiditi's sign).
- **Lung fissures** are usually visible in **lateral views** only.

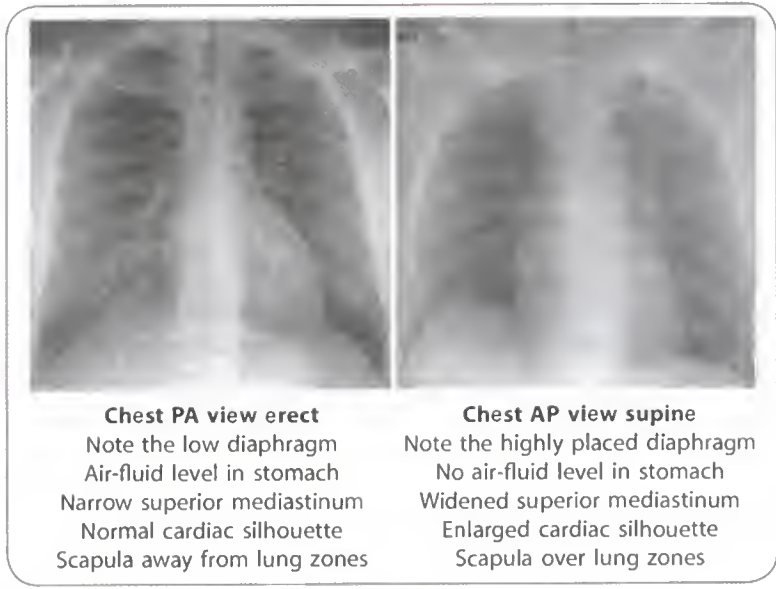


Fig. 30.17: Chest X-ray for demonstrating effects of various patient positioning

Felson's Silhouette Sign (Figure 30.18)

An intrathoracic lesion touching a border of the heart, aorta or diaphragm will obliterate that border on the chest radiograph; valuable **sign for localizing disease from the chest X-ray** as shown here:

Shadow of soft-tissue structure lost	Location of lung pathology
Ascending aorta and upper right heart border	Right upper lobe
Most of right heart border	Right middle lobe

Contd...

Shadow of soft-tissue structure lost	Location of lung pathology
Right hemidiaphragm	Right lower lobe
Aortic arch	Left upper lobe
Aortic knob and upper left heart border	Left upper lobe
Most of left heart border	Left lingula
Left hemidiaphragm	Left lower lobe

Contd...

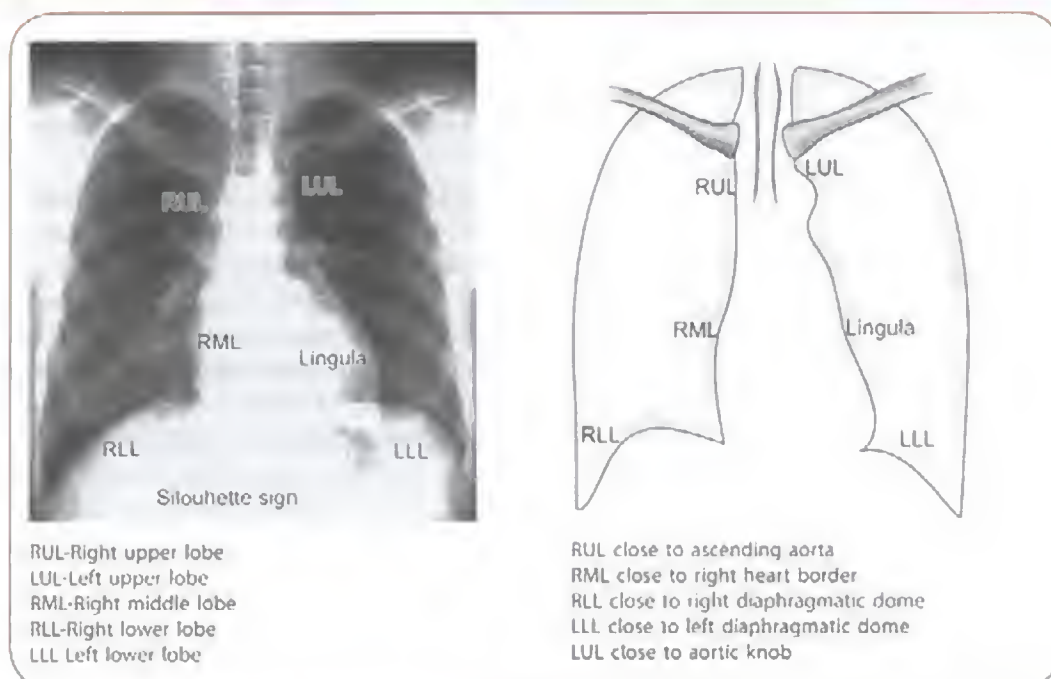


Fig. 30.18: Chest X-ray normal silhouette with adjacent lung segments

Egg Shell Calcification of Lymph Nodes

- Silicosis
 - Sarcoidosis
 - Lymphoma following radiotherapy
 - Coal miner's pneumoconiosis
- 'SILly SARAh LYMPed to the COAL MINE'



Fig. 30.19: Chest X-ray shows multiple enlarged bilaterally symmetrical hilar lymph nodes which show peripheral or egg shell calcification

Septal Lines (Kerley B Lines)

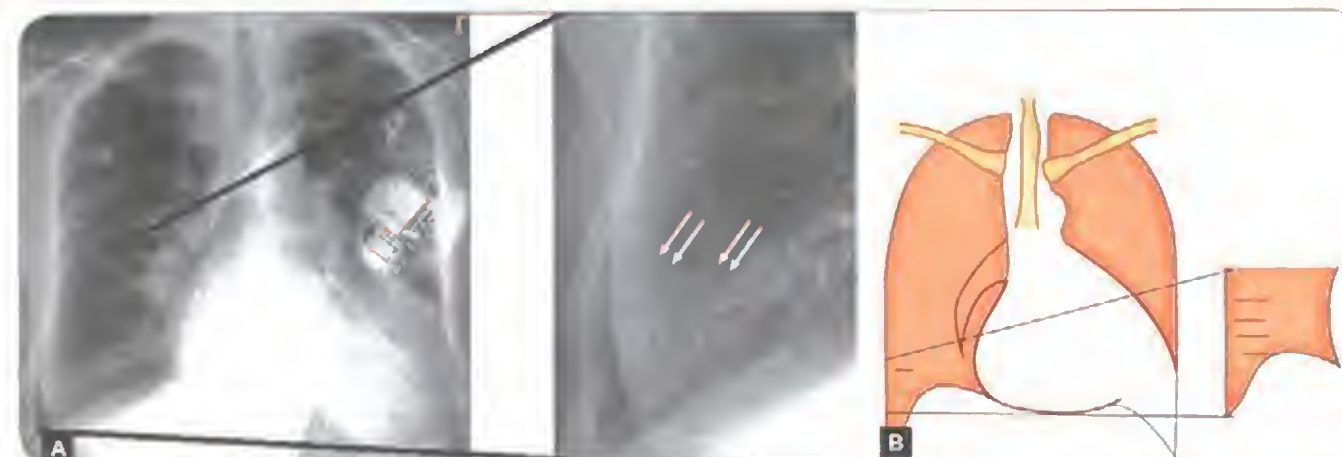
- Due to **visible interlobular lymphatics** extending from and perpendicular to the pleural surface; **best seen at the costophrenic angles**; unlike the blood vessels they often reach the edge of the lung (there are no visible vessels in the outer 1–2 cm of the lung). Seen in—
 - Pulmonary venous hypertension: **left ventricular failure (interstitial pulmonary edema), mitral stenosis.**
 - Lymphatic obstruction: **Pneumoconiosis, lymphangitis carcinomatosa.**

Kerley A Lines

Arcuate lines that radiate outward from the hila when more central interlobular septa become fluid-filled and radiographically apparent.

Kerley C Lines

A cubweb mesh of linear opacities in the middle portion of the lungs.



Figs 30.20A and B: Chest X-ray showing typical Kerley B lines. **Note:** The parallel transverse lines (arrows) perpendicular to pleural surface. The Kerley B lines are due to left ventricular failure in this case

Solitary Pulmonary Nodule (SPN)

- Neoplastic
- Malignant: Carcinoma bronchus, lymphoma, solitary metastases, carcinoid tumor
- Benign: **Hamartoma (popcorn calcification)**; lipoma, neurofibroma.
- Inflammatory: Granulomas (tuberculoma; histoplasma); lung abscess; rheumatoid nodule; vasculitides; Pneumonia (esp. pneumococcal), hydatid.
- Congenital: Sequestration; bronchogenic cyst; AV malformation; bronchial atresia with mucoid impaction
- Others: pulmonary infarction, hematoma, rounded atelectasis.

EXTRA EDGE

- Healed **Varicella pneumonia** is a/w **multiple** calcified nodules.
- Secondaries from osteosarcoma and chondrosarcoma show diffuse calcification.
- Investigation of choice for SPN. First choice is **Imaging-guided FNAC** or second choice is contrast **HRCT**.

Differentiating SPN on HRCT Scan

Benign SPN	Malignant SPN
• Smooth well-defined edge	• Irregular edge (corona radiata) and lobulated appearance
• Dense calcification in central, concentric, diffuse, popcorn or laminated pattern	• Size > 3 cm
• Fat within the lesion (specific for hamartoma)	• Spiculated margins and peripheral halo
• Lesions attached to vessels. Pleura or fissures	• Sparse calcification that is stippled, eccentric or amorphous
• Satellite lesion absent	• Cavitary lesions with thick wall (> 16 mm)
	• Pseudocavitation and air bronchogram with the lesion
	• Satellite lesion present

Miliary Mottling (Honeycomb Lung)

- Tuberculosis/fungal, tuberous sclerosis, neurofibromatosis; healed varicella pneumonia
 - Extrinsic: allergic alveolitis, cryptogenic fibrosing alveolitis
 - Metastases
 - Pneumoconiosis (esp. asbestosis), parasitic (Loeffler's syndrome, tropical eosinophilia)
 - Lymphangitis carcinomatosa, leukemia, lymphoma
 - Eosinophilic granuloma
 - Sarcoidosis
 - Collagen disorders (RA, scleroderma), cystic bronchiectasis, cystic fibrosis
 - Drugs: Nitrofurantoin, busulfan, cyclophosphamide, bleomycin and melphalan.
- 'TEMPLES CD'



Fig. 30.21: Multiple tiny spots distributed throughout the lung fields with the appearance similar to millet seeds. **Note** the normal background lungs, hila

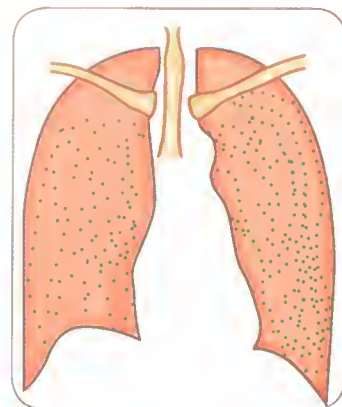


Fig. 30.22: Multiple tiny spots distributed throughout the lung fields with the appearance similar to millet seeds. No evidence of loss or increase in lung volume

Unilateral Hypertransradiant Hemithorax (Figure 30.23)

- **Rotation:** Poor technique, scoliosis
- **Chest wall:** *Poliomyelitis, postmastectomy, Poland's syndrome.*
- **Pleura:** *Pneumothorax*
- **Lung:** Compensatory/obstructive *emphysema*, unilateral bullae, McLeod's syndrome, congenital lobar emphysema.
- **Pulmonary vessels:** *Pulmonary embolus.*

Pneumatocoeles (Figure 30.24)

- One or more are filled thin-walled 'cysts' (may sometimes contain fluid levels); usually infective in origin; they appear during the first 2 weeks of the pneumonia and resolve within several months.
- **Infections:** *Staphylococcus aureus* (MC in childhood *Staphylococcal pneumonia*), also with *Pneumococcus*, *Klebsiella*, *E. coli*, *H. influenzae*, *Legionella*, *Pneumocystis jirovecii* (usually multiple and in the upper parts of the lungs, often leads to pneumothorax).
- **Traumatic:** Interstitial emphysema
- **Neoplastic:** Following treatment of pulmonary metastases (bladder cancer and germ cell tumors, may be visible only on CT).

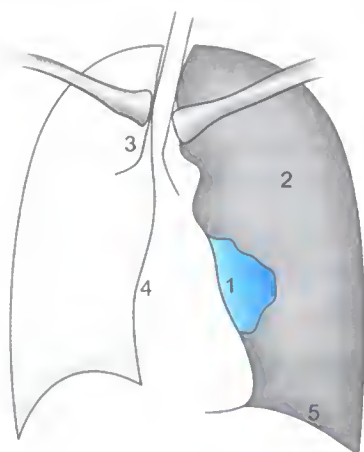
Pruning of Pulmonary Vasculature

- In **pulmonary arterial hypertension**, there is a redistribution of flow in the lungs from central to peripheral such that the peripheral vessels appear too small for the size of the central vessels from which they come. This discrepancy in the size of the central pulmonary vessels (which are large) compared to the peripheral pulmonary vasculature (which even though it is small is still indistinguishable from normal) is called **pruning**.



Chest X-ray PA view

Left side tension pneumothorax
Signs of push to right
Trachea and mediastinum are pushed to right side
Note the density difference between two sides, right side normal, left side hyperlucent



Signs of push

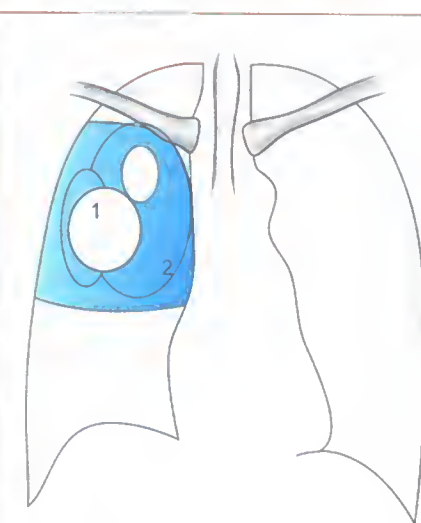
1. Collapsed left lung
2. Air under tension in left pleural cavity No bronchovascular markings
3. Tracheal shift to right side
4. Mediastinal shift to right side

Tension pneumothorax left side

Fig. 30.23: Chest X-ray showing tension pneumothorax



Chest X-ray of a child showing a pneumatocele multiple cavities, which developed over a period of 24 hours, seen in an area of consolidation. This is typical of *Staphylococcal pneumonia*



1. Multiple thin-walled cavities, of varying sizes, without any fluid level. The cavities developed acutely
2. Surrounding consolidation

Fig. 30.24: Chest X-ray showing pneumatocele

Rounded Atelectasis

- It occurs as a consequence of diseases with chronic pleural scarring, especially *asbestos-related pleural disease* and *TB*; most often at the *lung bases*, posteromedially; must be subpleural in position; it is asymptomatic BUT important because it resembles a bronchogenic carcinoma.
- **Imaging findings:**
 - **Rounded density** at lung base
 - Contiguous to area of pleural disease or superimposed on apparent asbestos-related pleural disease or TB
 - **Comet tail** on CT: Vessels and bronchi converge upon and appear to swirl around mass
 - **Crow's feet**—linear bands radiating from mass into lung parenchyma
 - Linear densities radiate back toward hilum
 - May have air bronchogram.

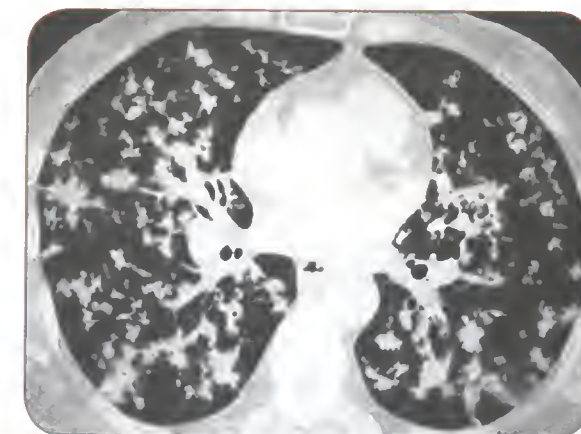


Fig. 30.25: Endobronchial spread in pulmonary Koch's on CT appear as poorly defined centrilobular rosettes of nodules, 2 to 10 mm in diameter, branching centrilobular opacities, described as 'tree-in-bud'

'Tree-in-Bud' Opacities on Chest X-ray/CT Scan

- The **tree-in-bud sign** describes the CT appearance of multiple areas of centrilobular nodules with a linear branching pattern.
- **Infections (MC):** Bacterial pneumonia, TB, nontuberculous mycobacterial infection, fungal and viral bronchiolitis.
- Lymphoma.

Signs of Pulmonary Hydatidosis on Chest X-ray

- **Meniscus/crescent sign:** As the cyst enlarges, it erodes bronchioles. Air is introduced between the pericyst and laminated membrane and appears as a thin, lucent crescent in the upper part of the cyst—the crescent or meniscus sign or perivesicular pneumocyst. It is a sign of impending rupture and is an indication for urgent thoracotomy.

- **'Water-lily', 'iceberg' or 'camelote' sign:** When completely collapsed, the crumpled endocyst floats freely in the most dependent part of the pericyst cavity.
- **'Rising sun' sign:** Daughter cysts may, rarely, be present, and the appearance of a round daughter cyst in the lowest part of the cavity resembles the rising sun.
- **Cumbo's sign:** When the parasite itself ruptures and air enters it, the endocyst is outlined by a double arch of air.
- **'Onion peel' sign:** CT may show an onion-peel appearance.
- **'Serpent' sign.**
- **'Whirl' sign.**



Fig. 30.27: X-ray chest shows consolidation lingular segment

Chest X-ray of Child with Foreign Body (FB) Aspiration

- **CXR** may be *normal* also.
- **Radiopaque FBs** are easy to diagnose.
- With **radiolucent FBs**, secondary radiographic signs are shown here:
 - **Obstructive emphysema** (hyperaeration of affected lung due to air trapping by ball valve effect of FB),
 - **Atelectasis**
 - **Pneumonia**, and
 - **Shifting of the mediastinum** away from the affected lung on expiratory CXRs
- Inspiratory and expiratory films comparing the relative deflation of the two lungs may demonstrate unilateral air trapping indicative of a foreign body.

Air Bronchogram

- Air bronchogram refers to the phenomenon of air-filled bronchi (dark and not normally visible) being made visible by the opacification of surrounding alveoli (grey/white).
- It is almost always caused by a **pathologic airspace/alveolar process**, in which something other than air fills the alveoli.
- Air bronchograms will not be visible if the bronchi themselves are opacified (e.g. by fluid) and thus indicate patent proximal airways.
- **Dark/Black bronchus sign**—is the appearance of relatively darker bronchus to the adjacent ground glass opacity. If the ground glass opacity progresses to consolidation, air bronchogram will be seen. This sign is used to identify ground glass opacity on HRCT in cases of *Pneumocystis jirovecii* pneumonia.



Fig. 30.26: X-ray chest show—pleural effusion in left pleural sac

Rib notching

Superior surface

Connective tissue diseases: RA, SLE, scleroderma, Sjogren's syndrome
Metabolic: hyperparathyroidism
Miscellaneous: Neurofibromatosis, Marfan's syndrome, restrictive lung disease, osteogenesis imperfecta, progeria, poliomyelitis

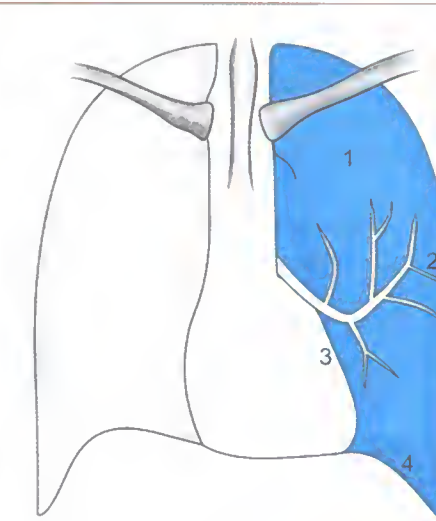
Inferior surface

Arterial: COA (Dock sign^o), aortic thrombosis, subclavian obstruction
Venous: SVC obstruction
Arteriovenous: pulmonary or chest wall arteriovenous malformation
Neurogenic: neurofibromatosis



Homogenous opacity left upper and mid zones

1. Air bronchogram
2. Loss of left heart border silhouette
3. Left dome diaphragm well seen
4. No evidence of push/pull
5. Normal CP angles
6. No volume loss



No signs of push/pull

1. Homogenous opacity left side thorax
 2. Classic air bronchogram
 3. Loss of left heart border silhouette
 4. Left diaphragm dome well seen
- Consolidation left lung upper lobe including lingular segment

Fig. 30.28: Chest X-ray to show air bronchogram signs

- Air bronchograms can be seen with several processes:
 - Pulmonary **consolidation (MC)**
 - Pulmonary **edema**
 - Nonobstructive **atelectasis**
 - Severe **interstitial lung disease**
 - Neoplasms: *bronchioloalveolar carcinoma*; *pulmonary lymphoma*
 - Pulmonary infarct
 - **Normal expiration**
- Increased anteroposterior diameter of chest.
- Widely spaced ribs, sternal bowing, tenting of the diaphragm, **saber-sheath** trachea, **bulla** formation.

Vascular Changes

- **Paucity** of blood vessels, often distorted.
- Pulmonary arterial hypertension: Pruning of peripheral vessels, increased caliber of central arteries, right ventricular enlargement.

EXTRA EDGE

- **HRCT** is **most sensitive** for imaging of **emphysema**.

More High Yield Points

Emphysema Radiology

Hyperinflation on X-ray

- **Flattened hemidiaphragm(s):** Most reliable sign—midpoint of right hemidiaphragm below or at the level of anterior end of 7th rib.
- **Low diaphragm**—Dome of diaphragm lying less than 1.5 cm above straight line drawn from costophrenic junction and vertebrophrenic junction.
- **Widened retrosternal airspace**—space between ascending aorta and sternum (3 cm below the manubrium) more than 2.5 cm on lateral film.
- **Costophrenic angle** of **more than 90°** on lateral film.
- Increased and usually irregular radiolucency of the lungs.

- **Hydropneumothorax** is a term given to the concurrent presence of a pneumothorax as well as a hydrothorax (i.e. air and fluid) in the pleural space. On an erect CXR, it is classically seen as an **air fluid level**.
- Primary pulmonary neoplasm producing **extensive mediastinal adenopathy** most significant radiographic finding: **Small cell carcinoma**.
- **Adrenals** should always be imaged in suspected bronchogenic carcinoma (since **adrenal metastases** are common in **small cell lung cancer**).

- **Aortopulmonary window** is the space under aortic arch and above superior border of left pulmonary artery—best visible on **left lateral** chest X-ray.
- Uremic lung – pulmonary edema
- **Pulmonary contusion** is the MC sequel of blunt chest trauma.
- ARDS: CXR shows diffuse or **patchy bilateral infiltrates** that rapidly become confluent; these **characteristically spare the costophrenic angles**.
- Pleural calcification – asbestosis; pleural fibroma
- Pulmonary mycetomas on radiographs most commonly show as lucent crescent.



Fig. 30.29: CXR showing noncardiogenic pulmonary edema in acute respiratory distress syndrome case with bilateral fluffy opacities. To note absence of pleural effusion and cardiomegaly



Fig. 30.30: X-ray chest of another patient shows small right sided hydropneumothorax (black arrow is hydrocomponent and white arrow is pneumocomponent)

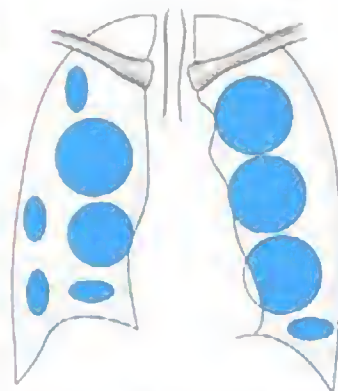
CARDIOVASCULAR SYSTEM

Heart Borders on CXR

- **Right border:** Formed by the right atrium mainly; also by SVC, IVC.
- **Left border:** Formed by aortic arch, main pulmonary artery, aortic knuckle, left atrial appendage (pulmonary bay), left ventricle.
- **Aortic nipple** on PA view—due to **left superior intercostal vein**.



Typical cannon balls
Multiple, well-defined round masses seen in both lung zones. The masses are of different sizes



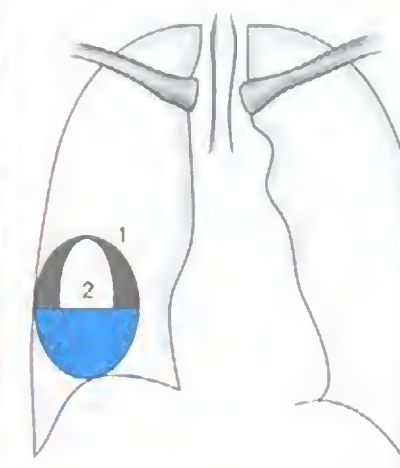
In a patient with known malignancy elsewhere in the body these findings are secondaries unless otherwise proved

Fig. 30.31: Chest X-ray showing multiple large masses



Chest X-ray in erect PA view

There is a large cavity with a horizontal fluid level indicating infected cavity
The cavity is located in the right lower zone



Lung abscess

1. Thick walled cavity
2. Air/fluid level indicating abscess formation

Fig. 30.32: Chest X-ray showing lung abscess



Fig. 30.33: Posterior anterior radiograph of chest demonstrating mediastinal contours

Mitral Stenosis

- **Straightening of the left border** of the cardiac silhouette
- **Double atrial shadow** (left atrial enlargement)
- **Prominent upper zone pulmonary veins** (inverted moustache sign/Antlers horn sign)
- **Prominence of the main pulmonary arteries**
- **Backward displacement of the esophagus** (due to enlarged left atrium)
- **Kerley B lines** (when left atrial pressure exceeds 20 mm Hg)
- **Prominent left atrial appendage** (aka 'fourth mogul'—due to enlarged left atrium)

- **Splaying of the subcarinal angle** ($> 120^\circ$ due to enlarged left atrium)
- **Protrusion of the right (!) cardiac border** (due to enlarged left atrium).



Fig. 30.34: X-ray chest in mitral stenosis. Double density due to enlarged left atrium (white arrow) is seen and there is increased carinal angle (black arrow). Normal carinal angle is $40-65^\circ$. The left heart border is straightened. There is prominence of upper lobe vessels in the lungs as appreciated by increased density in upper lobes

Cardiac Calcification

- **Pericardial:** *TB pericarditis* is MC cause; post-traumatic, postoperative; uremia.
- **Myocardial:** *Calcified myocardial infarct* is MC cause, aneurysm, postmyocarditis (especially rheumatic fever), hydatid.
- **Intracardiac:** Calcified valve, calcified thrombus, atrial myxoma, carcinoid syndrome.

Congestive Heart Failure

Stage I: Vascular phase, Pulmonary venous Hypertension, Redistribution phase

- Dilated, prominent upper lobe blood vessels—**cephalization**—earliest feature.
- Cardiomegaly
- Increased pulmonary artery to bronchus ratio—**broad vascular pedicle**
- Mediastinal width increases.

Stage II: Interstitial phase

- Kerley **B** lines
- Peribronchial cuffing (*bronchial wall thickening from interstitial edema*)
- Perihilar haze
- Thickened Interlobar fissure

Stage III: Alveolar phase

- Alveolar edema in basal and central regions (*Bat's wings or butterfly pattern*) or acute edema
- Ground glass appearance or cottonwool appearance
- Air bronchogram
- Pleural Effusion (bilateral)
- Consolidation.



Fig. 30.35: Bat's wings or butterfly pattern

Double Density Signs in Radiology

- **Double density sign (cardiac)**—right side of the left atrium projecting through the right atrium into the adjacent lung—a sign of left atrial enlargement.
- **Double-density sign (shoulder)**—on a standard anteroposterior radiograph of the shoulder and a cortical irregularity on the supraspinatus outlet view are highly suggestive of an *os acromial*. An *os acromial* results from the failure of fusion of the acromial secondary centers of ossification.
- **Double density sign (skeletal)**—Appearance of bone on bone scans in patient with *osteoid osteoma*.
- **Double density sign (spine)**—Intervertebral disk displacement on myelography.

Coarctation of Aorta

- Rib notching is *unusual before 10 years* of age. Affects 4 to 8th ribs **inferior borders** bilaterally.
- Unilateral and left-sided if associated with an anomalous right subclavian artery distal to the coarctation.
- Unilateral and right-sided if the coarctation is proximal to the left subclavian artery.
- Other signs include '**3 sign**' on CXR (a prominent ascending aorta and a small descending aorta with an intervening notch); on barium swallow of esophagus, the same is seen as '**reverse 3 sign or E sign**'.
- **MRI** is investigation of choice for coarctation (preoperative assessment and postoperative long-term follow-up).



Fig. 30.36: X-ray chest shows rib notching on the inferior aspect of the posterior 4 to 7th ribs

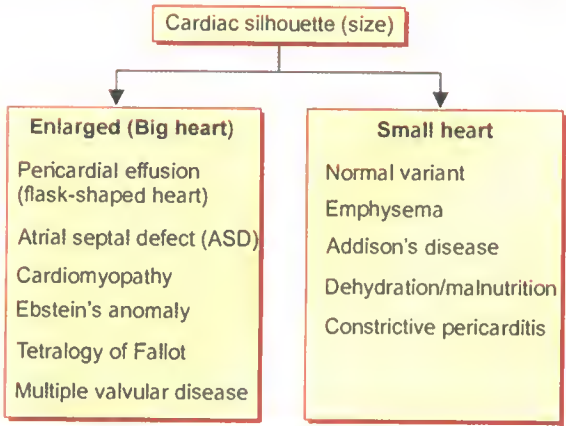


Fig. 30.37: Lucency beneath the right dome of diaphragm suggests free intraperitoneal air secondary to perforation of hollow viscus

GASTROINTESTINAL SYSTEM

Pneumoperitoneum

- Causes: Perforation; Peptic ulcer; hollow viscus perforation.
- **Plain X-ray chest PA view** is the best view to show a small pneumoperitoneum. *Can detect as little as 1 mL of air.* Can take **10 minutes** for all gas to rise.
- In patients unable to stand, **left lateral decubitus view** with *horizontal beam* is the view of choice.
- **CT scan** is the **most sensitive** investigation.
- Signs of pneumoperitoneum are given here:

- Bowel related signs**
 - **Rigler sign** (bowel wall outlined by air on the inside and outside).
 - **Telltale triangle** sign
- Right upper quadrant signs**
 - Hyperlucent liver sign
 - Anterior superior oval sign
 - Fissure for ligamentum teres sign
 - Visible gallbladder sign
 - Dodge cap sign
 - Hepatic edge sign
 - Dolphin sign
- Peritoneal ligament related signs**
 - Falciform ligament sign
 - Extrahepatic ligamentum teres sign
 - Inverted V sign
 - Urachus sign
- Other signs**
 - **Cupola** sign: Arcuate lucency overlying the lower thoracic spine.
 - **Drooping lily sign:** Liver, stomach and spleen are separated from diaphragm by intervening air.
 - **Football sign** (large pneumoperitoneum outlining the entire abdominal cavity).

Intestinal Obstruction

- On plain X-ray abdomen, jejunum is characterized by valvulae conniventes that pass from the antimesenteric to mesenteric border, spaced regularly giving rise to a *concertina effect* ('stack of coins').
- Ileum is described as '**characterless**' *loop of Wangensteen*
- Large intestine (the caecum excepted) shows haustrations, spaced irregularly and the indentations are not placed opposite one another.

Acute Intussusception

- Plain X-ray reveals *increased gas shadows in the small intestine*, and at times an *absence of the caecal gas shadow*.
- '**Claw sign**' or '**pincer shaped ending**' or '**coiled spring deformity**' or '**pitch fork sign**' in barium enema is seen.
- CT shows bowel within bowel—'**target**' appearance.



Fig. 30.38: Barium enema X-ray showing claw sign in intussusception

Ileocaecal TB

- **Fleischner sign:** Wide gap between thickened patulous ileocaecal valve and **narrowed ulcerated terminal ileum**; **‘inverted umbrella’** defect.
- **Stierlin’s sign:** Rapid emptying of narrowed terminal ileum into **shortened, rigid and obliterated cecum** on barium examination.
- Symmetrical annular **napkin ring stenosis** and **widened ileocecal angle (obtuse angle)**.
- **Transverse**, stellate ulcers with elevated margins are seen.

Carcinoma Head of Pancreas

- Barium meal shows **‘Frostburg’s inverted 3’** sign and **‘Rose thorning’** of duodenum.
- ERCP: **‘Scrambled egg’** appearance.
- CT, US and ERCP: **Double duct’ sign:** A tumor of the pancreatic head often obstructs both the pancreatic duct and the common bile duct, dilating both of them.

Adrenal Calcification

- **Wolman disease** (AR, lysosomal storage disease, hepatosplenomegaly, malabsorption with steatorrhea, **adrenal calcification**, MR, fatal early in life)
- Hemorrhage
- 2° to sepsis – **Waterhouse-Friedrichson syndrome**
- Adrenal cyst, adrenal neoplasms (rare)
- **Perinatal/neonatal hypoxia or birth trauma**
- **Addison disease; TB, histoplasmosis.**

Thumbprinting in Colon

- Intestinal inflammations (Colitides)
- **Ischemic colitis**—commonest at **splenic flexure**.
 - Ulcerative colitis, Crohn’s disease
 - Pseudomembranous colitis
 - Amoebic colitis
 - Schistosomiasis
 - Neoplastic: Lymphoma, metastases.

Benign and Malignant Gastric Ulcers Compared

Benign gastric ulcer	Malignant gastric ulcer
<ul style="list-style-type: none">• Regular smooth margin• Flat, smooth base often filled with whitish exudates• Normal radiating mucosal folds toward ulcer crater	<ul style="list-style-type: none">• Irregular raised margin• Ulcerated mass protruding into lumen• Thickened distorted folds do not reach ulcer edge

Contd...

Contd...

Benign gastric ulcer	Malignant gastric ulcer
<ul style="list-style-type: none">• Hampton’s line: A thin, sharply demarcated line with parallel, straight margins at the base of a benign gastric ulcer crater.	<ul style="list-style-type: none">• Kirklin complex: Heaped margins of the malignant gastric ulcer, which touch. This projects as a lucent rim around the ulcer on barium meal with compression of anterior abdominal wall.• Carman’s meniscus sign: Semicircular (meniscoid) configuration of malignant gastric ulcer seen in profile with compression of anterior abdominal wall

Radiological Features of Sigmoid Volvulus

- **Bird’s beak or bird-of-prey sign:** Single contrast barium enema examination is adequate because the barium readily enters the empty rectum and usually encounters a complete stenosis which is likened to a beak.
- A markedly distended sigmoid loop, which assumes a **bent inner tube or inverted U-shaped** appearance, with the limbs of the sigmoid loop directed toward the pelvis.
- **Coffee bean sign:** The involved bowel walls are edematous and the contiguous walls form a dense white line on radiographs. This line is surrounded by the curved and dilated gas-filled lumen resulting in a coffee bean-shaped structure.
- **Liver overlap sign:** The colonic haustra are lost, and progressive distension elevates the sigmoid loop under one of the diaphragms.
- **Northern exposure sign:** A dilated sigmoid colon that ascends to the transverse colon is said to be reliable sign of sigmoid volvulus on a supine abdominal radiograph.

More High Yield Points

- **Dieulafoy’s disease:** A rare cause of massive upper GI hemorrhage, due to erosion of an abnormally enlarged submucosal artery, typically in the **proximal stomach**.
- **Hiatus hernia** will show a characteristic **retrocardiac density with air fluid** levels.
- **Videofluoroscopy** is the **‘gold standard’** for diagnosis of **swallowing disorders**.
- **X-ray abdomen supine** is used in diagnosis of **intestinal obstruction**.

- **Dromedary hump:** Sometimes the **spleen causes an impression** on the upper lateral aspect of the left kidney, which is referred to as Dromedary hump.
- **Oral cholecystography** is also called Graham Cole test; should not be used when plasma bilirubin level is over 3 mg/100 mL.
- **Normal gallbladder wall** thickness on U/S is usually less than 3 mm.
- **Postoperative T tube cholangiogram** is performed 10–14 days after choledochotomy.
- Best investigation to detect a **4 mm nodule in pancreas** is **endoscopic ultrasound**.
- The only reliable sign that **differentiates large from small intestine** on **X-ray** abdomen is the presence of **feces**.
- **Barium** swallow—**serpiginous** filling defects—suggests **esophageal varices**.

URINARY SYSTEM

Must Know Signs

- **Ureterocele:** Adder head OR Cobra head deformity
- **Flower vase appearance:** Horseshoe kidney
- **Spider leg appearance:** Polycystic kidney
- **Golf hole ureter:** TB urinary bladder
- **Thimble bladder:** TB urinary bladder
- **Fish hook (J-shaped or hockeystick) ureter:** BPH
- **Bladder diverticulum:** Micturition may occur twice one after the other
- **Chalice (Bergman) sign:** Dilatation of ureter distal to neoplasm; not seen with calculi or thrombi
- **Rim sign in nephrogram:** Severe hydronephrosis
- **Rim and Ball nephrogram** on IVU seen in chronic obstructive nephropathy.
- **Soap bubble appearance:** Severe hydronephrosis
- **‘Splenic hump’** is an important variant causing: A bulge of the renal outline in IVU.
- **Bladder wall calcification resembling fetal head** seen in: **Schistosomiasis**

Bladder Calcification

- **In the lumen:** **calculus, foreign body** (encrustation of the balloon of a Foley catheter).
- **In the wall:** **Schistosomiasis** (bladder calcification classically resembles **fetal head!**), TB, transitional and squamous cell carcinoma, cyclophosphamide-induced cystitis.

Duplex Renal Collecting Systems/Duplex Ureter

- **Drooping lily sign:** Compression of lower moiety calyx. (D/D for drooping lily sign is **upper pole renal mass/ cyst**).

- **Weigert-Meyer rule:** When there is a complete duplication, the lower pole ureter inserts normally into the bladder and the upper pole ureter inserts ectopically into the bladder **medially** and **caudal** to the insertion of the lower pole ureter.

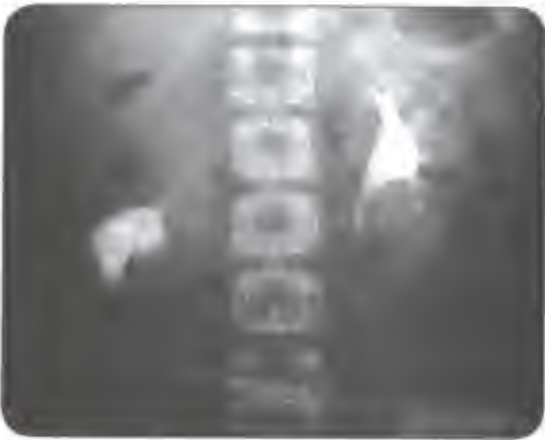


Fig. 30.39: Duplex right kidney. IVU shows that the upper moiety is non-functioning and displaces the lower pelvicalyceal system downwards, producing the ‘drooping lily sign’

Causes of Teardrop (Pear-shaped) Bladder

- Pelvic fluid: **Pelvic hematoma**; bilateral lymphoceles; extravasated urine/bilateral urinomas; pelvic abscess, pelvic lipomatosis
- Vascular dilatation: Bilateral iliac artery aneurysms; inferior vena cava (IVC) occlusion
- Symmetric lymph node enlargement, e.g. lymphoma, leukemia
- Psoas muscle hypertrophy

Ultrasound Features of Acute Pyelonephritis

- Particulate matter in the collecting system
- Reduced areas of cortical vascularity by using power Doppler
- Gas bubbles (emphysematous pyelonephritis)
- Abnormal echogenicity of the renal parenchyma
- Focal/segmental hypoechoic regions
- Diffuse or focal enlargement of kidney
- Extrarenal fluid collections (pus in the perinephric space).

More High Yield Points

- **Ureter**, normally on ultrasound should not be more than 7 mm in diameter, but pregnancy and OCPs can cause moderate dilatation.
- In **intravenous urogram (IVU)**, visualization of the renal substance (**nephrogram**) is dependant on the amount of contrast reaching the kidneys, whereas

visualization of collecting system (*pyelogram*) depends mainly on the ability of kidneys to concentrate urine.

- In injury to the kidney, **intravenous urogram (IVU)** should be done immediately.
- **Renal arteriography** is performed via a catheter introduced into the femoral artery by the **Seldinger technique**.
- **Earliest finding of renal TB on IVU is calyceal erosion** (loss of calyceal sharpness due to mucosal edema).
- Inv. of choice for **early renal TB is IVU**; for advanced renal TB is CT scan.
- **Stipple sign** refers to the pointillistic end-on appearance on **intravenous pyelography** of contrast material tracking into the interstices of a papillary lesion—seen in **transitional cell carcinoma**.
- **Posterior urethral valves** occur frequently in **young boys** and are best demonstrated by **micturating cystourethrogram (MCU)**.
- Investigation of choice for **ureteric stones** in **non-contrast CT scan**.

SKULL AND BRAIN

Normal Intracranial calcification	Abnormal intracranial calcification
<ul style="list-style-type: none">• Choroid plexus• Falx cerebri• Interclinoid ligament• Lateral edges of diaphragma sellae• Petroclinoid ligament• Pineal body	<ul style="list-style-type: none">• Lipoma of corpus callosum (<i>bracket like</i>)• Oligodendroglioma (<i>serpentine</i>)• Sturge Weber syndrome (<i>tram track</i>)• Meningioma (<i>ball like</i>)• Dermoid (<i>arc calcification</i>)• Craniopharyngioma (<i>punctate/curvilinear</i>)• Neurocysticercosis (<i>rice grain</i>)• CMV (<i>periventricular</i>)• Toxoplasmosis (<i>scattered flakey</i>)

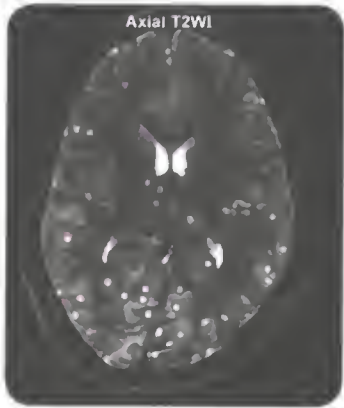


Fig. 30.40: Rice grain calcification in neurocysticercosis

Ring-Enhancing Lesion on CT Scan

‘MAGIC DR LT’: Metastases, Abscess—pyogenic, tuberculoma, Glioblastoma multiforme, Infarct (subacute phase), Contusion, Demyelinating disease, Resolving hematoma, Lymphoma, Toxoplasmosis.

Basal Ganglia Calcification

- **Endocrine:** Hyperparathyroidism/ypoparathyroidism-pseudohypoparathyroidism
- **Metabolic:** Fahr syndrome, Cockayne syndrome, Leigh disease
- **Idiopathic (MC)**, bilateral and symmetrical
- Birth anoxia
- Toxoplasmosis/CMV—usually not limited to basal ganglia.

J-shaped Sella Turcica

- Optic chiasm glioma
- Neurofibromatosis
- Mucopolysaccharidoses (Hurler’s syndrome)
- Mild arrested hydrocephalus
- Achondroplasia
- Chronic hydrocephalus

Raised ICT; X-ray Signs

- **In children:** *sutural diastasis* (*first and most prominent*); *increased convolitional markings* (*copper beating of skull*).
- **In adults:** Thinning or *erosion of anteroinferior dorsum sellae*; (*first and most prominent*); pineal displacement.

Must Know Signs

- **Open ring sign:** Specific for demyelination
- **‘Winking owl’ sign:** Erosion of the pedicles; the earliest radiologic sign of vertebral tumor/mets.
- **Ballooning of pituitary fossa:** Tumors of pituitary
- **Bare orbit appearance:** Neurofibromatosis
- **Blueberry muffin sign:** Raised purple skin lesions, suggestive of dermal metastases of neuroblastoma
- **Chiari II malformation:** **Lemon** sign (infolding of the frontal bones) and **Banana** sign (cerebellar deformity)
- **Moth eaten skull:** Syphilis
- **Suprasellar calcification:** Craniopharyngioma (MC cause in children also)
- **Sunburst periostitis:** Midline subfrontal meningioma
- **Tuberculoma:** MC site in brain is posterior cranial fossa
- **‘Sail shape’:** Characteristic shape of **thymus** in young children

Must Know Signs

- **Panda sign:** Appearance of the midbrain, when the red nucleus and substantia nigra are surrounded by high T2 signal; classically seen in **Wilson disease**.
- **Ice cream cone sign:** In **acoustic schwannoma**.
- **Racing car sign:** Widely spaced lateral ventricles in **agenesis of corpus callosum**.
- **Krabbe’s disease:** **Hyperdense basal ganglia** and **hypodensity of the white matter** is diagnostic on **CT scan**.
- **Hair on end skull:** **Thalassemia**
- **Mesial temporal sclerosis:** aka **hippocampal sclerosis**—investigation of choice is **atrophy of the hippocampus, fornix and mamillary body**.
- **Trouser leg appearance** on ascending myelogram—seen in **intramedullary tumor**.
- Molar tooth sign: Joubert syndrome

National Institute for Health and Clinical Excellence (NICE) Guidelines for Computed tomography (CT) in Head Injury

- GCS <13 at any point
- GCS 13 or 14 at 2 hours
- Focal neurological deficit
- Suspected open, depressed or basal skull fracture
- More than one episode of vomiting
- Any patient with a mild head injury over the age of 65 years or with a coagulopathy, for instance warfarin use, should be scanned urgently
- Dangerous mechanism or injury or antegrade amnesia >30 minutes warrants CT within 8 hours.

EXTRA EDGE

Signs of **basal skull fracture** = **hemotympanum**, **‘panda’** eyes (bruising around the eyes), CSF leakage (ears or nose) or **Battle’s** sign (bruising behind the ear).

More High Yield Points

- **Primary CNS tumors** that commonly metastasize through the CSF to cause leptomeningel seeding **‘drop metastasis’:** Medulloblastoma, ependymomas, malignant gliomas and primitive neuroectodermal tumors (PNET).
- **The position of the calcified pineal gland** is the only method of identifying the **midline on plain skull films**.
- **T2 hyperintensity in the thalamus** seen as **Pulvinar sign** and **Hockey stick sign** in **variant Creutzfeldt jakob disease**. (Note: Hockey stick sign also in **thyroid hemiagenesis**).

- **Puff of smoke appearance** on cerebral angiography is seen in **Moyamoya disease**.
- Spinal cord injury without radiographic abnormality (SCIWORA)—MC seen in children.
- **Larynx is best examined with MRI**.
- Investigation of choice following **acute** head injury - **noncontrast CT scan**.
- Investigation of choice for **leptomeningeal carcinomatosis** is **contrast enhanced MRI**.

OBSTETRICS AND GYNECOLOGY

Ultrasound of Ectopic Pregnancy

- Only **diagnostic finding is the presence of a live embryo outside the uterus** (presence of fetal heart motion outside the uterine cavity).
- **Free fluid** in the pouch of Douglas.
- Endometrial thickening (decidual cast, pseudogestational sac).
- Adnexal mass may be seen.

Blighted Ovum (Anembryonic Pregnancy)

- A fertilized ovum in which embryonic development has been arrested. Development of a normal appearing gestational sac without an embryo.
- Ultrasound signs of an ‘Empty’ sac are:
 - No fetal parts seen with a sac diameter > 30 mm.
 - No yolk sac seen with a sac > 20 mm.
 - Irregular sac contour.

Ultrasound Signs of Ovulation

- Collapse of the follicle.
- Free fluid in the pouch of Douglas.
- Echo-free zone around the endometrium.

Radiology of Fetal Death

- **Robert’s sign**—appearance of gas shadows in the heart and great vessels may appear as early as 12 hours but difficult to interpret.
- **Spalding’s sign** - Overlapping of cranial bones on one another due to liquefaction of brain matter. Usually appears 7 days after fetal death.
- **Ball’s sign**—Hyperflexion of the spine is more common.
- **Deuel’s or Halos sign**—Elevation of pericranial fat.

Ultrasound Signs of Pregnancy

Twin peak sign	Presence of a dichorionic-diamniotic twin gestation (multiple gestation)—also called the lambda sign ; most useful in assessing the chorionicity of pregnancies after 10 weeks .
T sign	Denotes a monochorionic pregnancy ; (It is really the absence of a twin-peak sign)
Double decidual sac sign	Helps in distinguishing between an early intrauterine pregnancy and a pseudogestational sac .
Double bleb sign	It is an important feature of an intrauterine pregnancy and thus distinguishes a pregnancy from a pseudogestational sac or decidual cast cyst.
Interstitial line sign	Finding in interstitial ectopic pregnancy .
Tubal ring sign	Sign of a tubal ectopic pregnancy ; It comprises of an echogenic ring which surrounds an unruptured ectopic pregnancy
Empty amnion sign	Visualization of an amniotic sac without concomitant visualization of an embryo. It is an indicator pregnancy failure regardless of the mean sac diameter

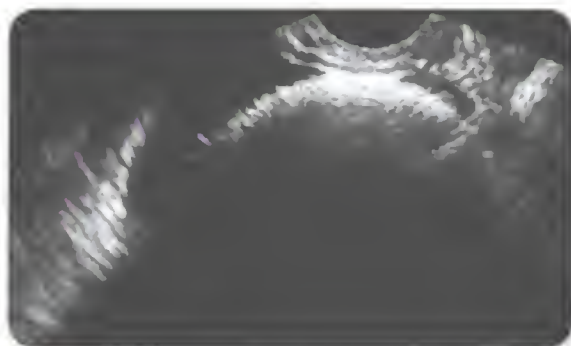


Fig. 30.41: 'Tip of iceberg' sign on ultrasound is seen in dermoid cyst of ovary; a highly echogenic mass with posterior shadowing is noted; the echogenic area hides the structures posterior to it

Contd.,

• Air crescent sign/ meniscus sign	Air is seen between the Aspergillus fungal ball and the wall of the cavity
• Mounier Kuhn syn.	Tracheomegaly, tracheobronchomegaly
• Pandora's pneumonitis	Extrinsic allergic alveolitis
• Popcorn calcification	Hamartoma lung
• Shrinking lung syn.	SLE
• Steeple sign on AP view neck	Croup (acute laryngotracheobronchitis)
• Thumb sign on lateral neck film	Acute epiglottitis
• V sign of Nacirio	Boerhaave's syndrome (indicates pneumomediastinum + pneumothorax)
• Vallecular sign	Retention of barium in hypopharynx seen in Ca larynx
• Spinnaker (angel wing) sign	Sign of pneumomediastinum seen on neonatal CXR; refers to the thymus being outlined by air with each lobe displaced laterally
• 'S sign of Golden' ('reverse S sign')	Convexity of the medial aspect of the minor fissure in patients with right upper lobe atelectasis usually due to a large central mass (a characteristic presentation of bronchogenic carcinoma)
• Linguine sign	MRI signs of intracapsular rupture of a breast implant
• Breast within a breast sign	Breast hamartomas (fibroadenolipomas) ; well-circumscribed benign lesions containing a mixture of fibrous, glandular and fatty tissue (just like normal breast), hence appears like a second breast sitting within a breast
• Reversed halo sign (atoll sign)	Central ground-glass opacity surrounded by denser consolidation of crescentic (forming more than three-fourth of a circle) or ring (forming a complete circle) shape of at least 2 mm in thickness; relatively specific sign for cryptogenic organizing pneumonia
• Panda sign	In sarcoidosis in a gallium-67 citrate scan; due to bilateral involvement of parotid and lacrimal glands in sarcoidosis, superimposed on the normal uptake in the nasopharyngeal mucosa
• Luftsichel sign	Peri-aortic knob hyperlucency in left upper lobe collapse

Contd.,

MORE RESPIRATORY ONE-LINERS

• Garland's triad (1-2-3 sign)	Lymphadenopathy pattern in sarcoidosis : Right paratracheal; right hilar and left hilar nodes
• Biello-Sigel criteria	Used for ventilation perfusion mismatch
• Bull's eye lesion in lung	Seen in granuloma
• Butterfly/bat's wing pattern	CXR finding in Pulmonary edema

MORE CVS ONE-LINERS

• Lambda sign	Small ascending aorta seen in hypoplastic left heart syndrome
• Cardiothoracic ratio	Should be normally less than half (i.e. 0.5)
• Coeur en sabot (boot-shaped heart)	Fallot's tetralogy
• Egg on side/string appearance	TGA —transposition of great arteries
• Egg in cup appearance	Constrictive pericarditis
• Pear heart	Pericardial effusion (a.k.a flask, money bag, water bottle)
• Snowman (figure of 8 heart)	TAPVC —total anomalous pulmonary venous connection
• Uhl disease shows	'Parchment right ventricle'; deficient right ventricular musculature
• Draped aorta sign	Posterior aortic wall is unidentifiable and follows the vertebral contour and associated with chronic contained rupture of an abdominal aortic aneurysm with vertebral erosion
• High attenuating crescent sign	Represents an acute hematoma or bleed within either the mural thrombus or the aneurysmal wall, especially when detected on unenhanced CT-scans; specific sign of impending abdominal aortic aneurysmal rupture (contained rupture)
• Cobweb sign and Beak sign	Arterial dissection
• Scimitar sign	The refers to a curved, tubular opacity adjacent to the right of the heart and extending toward the diaphragm seen on a frontal radiograph. Scimitar refers to a Turkish/Persian sword that has a curved blade—seen in scimitar syndrome (also hypogenetic lung or venolobar syndrome)
• Finger in glove sign	Seen on either chest X-ray or CT chest and is characteristic sign of a bronchocele .

MORE GIT ONE-LINERS

• Accordion sign	In pseudomembranous colitis ; due to oral contrast being trapped between edematous haustral folds and pseudomembranes formed on the surface of the colon
• Apple core appearance	Carcinoma of sigmoid colon (on barium enema)
• Arc of Buehler	Persistent embryologic anastomosis between celiac artery and superior mesenteric artery
• Arc of Riolan	Inconstant anastomotic artery between middle + left colic artery
• Bright liver on U/S	Fatty degeneration of liver
• Bull's eye lesion, gut	Lymphoma
• Bull's eye lesion, liver	Hepatic candidiasis
• Bull's eye lesion, stomach	Melanoma is MC cause
• Chain of lakes	Chronic pancreatitis, appearance on ERCP
• Chilaiditi's syndrome	Interposition of colon between liver and right hemidiaphragm causing elevation of right hemidiaphragm
• Cirrhosis of the liver	Signs on CT/US: Reduction in size of the right lobe of the liver with splenomegaly
• Sigmoid volvulus	'Coffee bean' sign, 'bird's beak' deformity or 'ace of spade' deformity
• Common bile duct (CBD)	Is dilated when it is more than 7 mm in diameter
• Corkscrew esophagus	Diffuse esophageal spasm
• Double bubble sign	Duodenal atresia
• Triple bubble sign	Jejunal atresia
• Floating membrane sign	Liver in hydatid disease
• Cartwheel appearance	On Ultrasound, is seen in hydatid disease
• Gallstones in 10% of cases	Seen as radio-opaque on plain X-ray
• Invertogram	Done to diagnose imperforate anus
• Acute cholecystitis	Iminodiacetic acid (IDA) labelled with ^{99m} Tc scans (HIDA, PIPIDA scans)
• Portal vein	Important landmark in hepatic anatomy

Contd.,

Contd...

- **Spleen** MC injured organ in blunt abdominal trauma
- **Perforated peptic ulcer** MC cause of spontaneous pneumoperitoneum
- **Medusa locks sign** Seen in children infested with roundworms
- **'Mercedes Benz' sign/Seagull sign** Radiolucent gallstone with gas in it
- **Chiba's needle** Needle used for percutaneous transhepatic cholangiography (PTC)
- **Pearl necklace gallbladder** Rokitansky Aschoff sinuses, adenomyomatosis of gallbladder
- **'Rose thorn' of medial wall of duodenum** Ca head of pancreas
- **'Saw tooth' appearance** Diverticulosis of the sigmoid colon on barium enema
- **Sandwich sign** Mesenteric adenopathy
- **'Shaggy' esophagus** Aggressive Candida esophagitis in AIDS
- **Small bowel obstruction** Triad of vomiting, abdominal distension and 'string of beads' sign on abdominal X-ray
- **'Thumbprinting' of colon** Ischemic colitis (due to submucosal edema); serrated mucosa is also seen
- **'Trifoliate' duodenum** Due to secondary duodenal diverticula which occurs as a result of scarring of ulcer
- **Spongy appearance with central sunburst calcification** Seen in serous cystadenoma of pancreas
- **Central dot sign** Seen in Caroli's disease



Fig. 30.42: Plain X-ray shows double bubble sign in the case of duodenal atresia



Fig. 30.43: Plain X-ray abdomen erect shows triple bubble sign



Fig. 30.44: Barium study showing thumbprinting suggestive of bowel ischemia (arrow)

MORE SKELETAL SYSTEM ONE-LINERS

- **Absent bow-tie sign** Loss of the normal appearance of the menisci on parasagittal MRI images, suggests meniscal injury
- **Anteater nose appearance** Calcaneonavicular coalition
- **Anterior cruciate ligament tear** Anterior drawer sign, bone bruise sign, deep lateral femoral notch sign seen in
- **Segond fracture** Is an avulsion fracture of the knee which involves the lateral aspect of the tibial plateau, a/w disruption of the anterior cruciate ligament

Contd...

Contd...

- **Calcification of meniscal cartilage** Pseudogout anterior
- **Calcification of IV disk** Alkaptonuria (ochronosis)
- **Calcification of interosseus membrane** Skeletal fluorosis
- **Cockade image** Intraosseous lipoma
- **'Corduroy cloth' appearance** Hemangioma of vertebrae; usually cavernous; Vertically striped orientation of bone trabeculae
- **Cupids bow contour** Normal spine
- **'Double line' sign on MRI** Avascular necrosis, commonly of the femoral head
- **Heel pad sign seen in** Acromegaly
- **Iliac horns are seen in** Nail-patella syndrome
- **Schmorl's nodes** Indentations of the IV disk into the endplates of the vertebral bodies
- **MELorheostosis** **Candle** bone disease (*Candle MELts!*)
- **Metacarpal sign** Turner's syndrome (*short fourth metacarpal*)
- **MC location for a unicameral bone cyst is the** Proximal humerus
- **O'Donoghue's unhappy triad** Anterior cruciate ligament tear, medial collateral ligament tear and medial meniscal tear
- **'Onion peel' diaphysis seen in** Ewing's sarcoma
- **Optic foramen enlargement suggest** Optic nerve glioma
- **Osteopathia striata** Striped bone disease
- **Osteopetrosis** Marble bone disease
- **OsteoPOikilosis** SPOTted bone disease
- **Pedestal sign** Prosthetic loosening of the femoral stem in cementless total hip arthroplasty
- **Physaliphorous cells are seen in** Chordomas
- **Scabbard trachea seen with** Tumor, other swellings which compress trachea
- **Soap bubble appearance seen** Osteoclastoma

Contd...

Contd...

- **'Sun ray' appearance, Codman's triangle seen in** Osteosarcoma
- **Tear drop sign (orbits) seen in** Blow out fracture of floor of orbit
- **Teardrop sign (ankle) seen in** Ankle effusion
- **Terry Thomas sign seen in** Widened space between the scaphoid and lunate bones on a frontal view of the wrist secondary to scapholunate dislocation
- **Trumpet sign seen in** Disk herniation (*enlargement of nerve root secondary to edema*)
- **Tumbling bullet sign seen in** Post-traumatic bone cyst
- **Wimberger's sign** Symmetrical focal bone destruction of the medial portion of the proximal tibial epiphysis (*seen in congenital syphilis*)
- **'Fallen fragment' sign** Seen in *solitary bone cyst*. Pathologic fracture of a simple bone cyst may give rise to a flake of bone (fragment) situated dependently in the fluid-filled cyst cavity.
- **Phemister's triad** TB arthritis: Periarticular osteoporosis, peripheral bony erosions and gradual narrowing of the joint space
- **Toothpaste sign** Represents an extrusion of a disc into epidural space
- **Blumensaat's line** Corresponds to the roof of intercondylar notch of the femur as seen on lateral radiograph of knee joint
- **Arachnodactyly** Seen in **Marfan's syndrome**; elongated and slender fingers and toes; The **metacarpal index** is increased in arachnodactyly *Normal range: 5.4–7.9; Arachnodactyly: 8.4–10.4.*
- **Driven snow appearance** **Pindborg** tumor (calcifying epithelial odontogenic tumor)
- **Windswept deformity** **Rheumatoid arthritis**, X-linked hypophosphatemic **rickets**, **Cerebral palsy**

X-RAY VIEWS

X-ray Views for Paranasal Sinuses

View	Features
Water's view (occipito-mental view)	Nose and chin touch the film ('sniffing a flower' position) and X-ray beam is projected from occipital side Open mouth view shows sphenoid sinus Maxillary sinus seen best in this view
Caldwell's view (occipito-frontal view)	Nose and forehead touch the film frontal and ethmoid sinuses seen well in this view Best view for superior orbital fissure
Lateral view	Best for sphenoid sinus and orbital roof



Fig. 30.45: X-ray paranasal sinus Water's view showing right side haziness in frontal, ethmoidal and maxillary sinuses (pansinusitis)
Source: Dr Jayesh Patel, Consultant Radiologist, Anand, Gujarat

X-ray Views for Temporal Bone

- **Law's view:** Lateral oblique view of mastoid; X-ray beam is projected 15° cephalocaudal; Key areas of mastoid - attic, aditus and antrum are not well seen.
- **Schuller's view:** Similar to Law's view; X-ray beam is projected 30° cephalocaudal.
- **Stenver's view:** Long axis of petrous bone lies parallel to the film.
- **Turner's view:** AP view of skull with 30° tilt from above and in front; both petrous pyramids can be compared.
- **Transorbital view:** Done for acoustic neuroma and petrous pyramid.
- **Submentovertical view.**

X-ray views for certain other conditions

- ▶ Ballcatchers and Brewerton's view: For X-ray signs of rheumatoid arthritis of hand
- ▶ Knee PA (weight-bearing): Rosenberg's view; for osteoarthritis knee.
- ▶ Anthosen's and Isherwood: Subtalar joint
- ▶ Cervical—Cervicothoracic view – Swimmer's view
- ▶ **Lateral decubitus:** For revealing minimal **pleural effusions** (can detect as little as 10 mL of pleural fluid!).
- ▶ **Lordotic:** for right middle lobe (lungula) of lung
- ▶ Reverse lordotic: To detect interlobar effusion
- ▶ **Apical lordotic:** For **apex** of lung
- ▶ **Skyline view:** **Patella** fracture
- ▶ **Stryker's view:** Recurrent subluxation/dislocation of shoulder
- ▶ Rhese view: Optic foramen.
- ▶ **Judet view:** Pelvis
- ▶ **Odontoid view:** Fracture of C1, C2
- ▶ **Von Rosen view** (hips fully abducted and externally rotated): Congenital dysplasia of hip
- ▶ Zanca view—Acromioclavicular joint
- ▶ Serendipity view—Sternoclavicular joint

MORE NAMED SIGNS

'Animal' and 'Food' Signs in Radiology

- **Fishtail deformity of the elbow:** Due to abnormal trochlear ossification following a distal humeral fracture in childhood.
- **Vertebral scalloping:** May be anterior or posterior border
- **Endosteal scalloping:** Medullary cavity masses, e.g. multiple myeloma
- **Lobster claw sign:** Of papillary necrosis
- **Swan neck deformity:** Of rheumatoid arthritis
- **Bird-beak sign:** Achalasia (also known as rat tail sign)
- **Beak sign:** Of arterial dissection
- **Beak sign of sigmoid volvulus**
- **Gull wing appearance:** Erosive osteoarthritis
- **Staghorn calculus:** Struvite renal calculi
- **Feline esophagus:** Horizontal striations seen on barium swallows as a variant of normal.
- **Eye of tiger sign:** Classical of Hallervorden-Spatz syndrome
- **Bear's paw sign:** Xanthogranulomatous pyelonephritis
- **Bear claw sign:** On contrast CT, in case of **hepatic lacerations**.
- **Hidebound sign:** Gastrointestinal scleroderma
- **Dural tail:** Of meningioma—do not know tail of which animal though
- **Cyclops lesion:** Usually post ACL repair

- **Medusa head:** Of a developmental venous anomaly (DVA) also a sign of severe portal hypertension
- **Cervical Hamburger sign:** Normal cervical facet joints on axial CT
- **Honeycomb lung:** UIP/pulmonary fibrosis
- **Mesenteric hamburger sign:** Mesenteric lymph node enlargement
- **Omental cake:** Metastases to omentum.
- **Sausage digit:** Underlying inflammatory arthritis or dactylitis
- **Head cheese sign:** Hypersensitivity pneumonitis
- **Leather bottle stomach:** Of linitis plastica (aka water bottle sign)
- **Hot cross Bun sign:** MRI appearance of pons in neurodegenerative diseases (**multisystem atrophy**; spinocerebellar atrophy types 2,3; variant CJD).

'Fruity' signs in radiology

- ▶ **Banana sign:** Chiari II malformation
- ▶ **Lemon sign:** Chiari II malformation
- ▶ **Sign**
- ▶ **Banana fracture:** Paget disease
- ▶ **Bunch of grapes sign:** Hydropic swelling of trophoblastic villi in gestational trophoblastic disease
- ▶ **Apple core sign—**colorectal carcinoma and synovial osteochondromatosis
- ▶ **Pear-shaped bladder** (pelvic hematoma)
- ▶ **Strawberry gallbladder:** Diffuse cholesterosis of gallbladder.
- ▶ **Strawberry skull:** Trisomy 18 (Edwards Syndrome)
- ▶ **Celery stalk metaphysis:** Osteopathia striata and congenital rubella infection

MORE HIGH YIELD ONE-LINERS

- **Steinstrasse:** The term (from German, meaning stone street) refers to the stream of tiny stone fragments that may fill the ureter after lithotripsy.
- **Picture Archiving and Communications System, (PACS),** enables images, such as X-rays and scans to be stored electronically and viewed on screens, so that doctors and other health professionals can access the information and compare it with previous images at the touch of a button.

- **Orthopantomogram:** An orthopantomograph is a panoramic radiograph machine that permits visualization of entire **maxillary, mandibular, TM joint** and contiguous structures on a single extraoral film—**curved radiographic cassette** is used.
- **'Magic angle phenomenon':** Collagen fibers oriented at 55° to the main magnetic field may result in increased signal within tendons or menisci. Awareness of this artefact avoids confusing it with a pathologic process.
- The first imaging modality that should be used to confirm the location of an **intrauterine device** is **ultrasound**.
- For pneumothorax, **Best view:** Plain X-ray chest PA view in full expiration
- Most radiodense substance is **bone**.
- **Cardiotoxicity** caused by radiotherapy and chemotherapy is best detected by **endomyocardial biopsy**.
- **Tritium** has a **half life** of 4500 days (**12 years**).
- Investigation of choice for **glass foreign body** is **plain X-ray** (since glass is always radiopaque).
- **Wedge angle** is the angle between the 50% isodose curve and the normal to the central axis.
- **Periosteal reaction is uncommon with metastases except with neuroblastoma.**
- **Best method** to confirm positioning and integrity of **ICD** (implantable cardioverter defibrillator) is **chest X-ray**.
- **Epiphyseal dysgenesis** is seen in **hypothyroidism**.

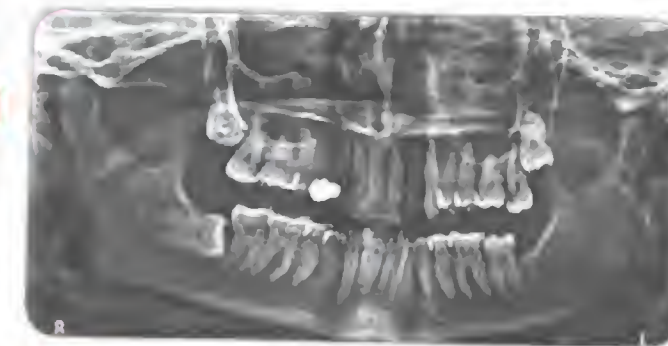


Fig. 30.46: Orthopantomogram: Impacted molars
Source: Dr Jaydeep Doshi, Consultant Radiologist, Anand, Gujarat

Radiotherapy

TYPES OF IONIZING RADIATION

Type	Mass	Charge	Comment
Electromagnetic			
X-ray	0	0	X-rays and gamma rays DO NOT differ except in the source. X-rays are produced mechanically (by deceleration of fast moving electrons)
Gamma rays	0	0	Gamma rays are produced by nuclear disintegration of radioactive isotopes. X rays are MC used for radiotherapy.
Particulate			
Electron (e)	9.1×10^{-31} kg	-1	Electron beam radiotherapy (beta rays) used in mycoses fungoides, skin tumors
Proton (p)	$2000 \times e$	+1	Exhibits a Bragg peak
Neutron (n)	$2000 \times e$	0	CANNOT be accelerated by electrical field
Alpha particle (2p + 2n)	$8000 \times e$	+2	Helium nucleus
Beta particle		-1	Equivalent to electron

Particle emitters

Alpha particle emitters	Beta particle emitters	Gamma rays emitters
Uranium	Yttrium 90	Cesium 137
Thorium	Phosphorus 32	Cobalt 60
Actinium	Strontium 90	Iodine 131
Radium	Samarium-153	Radium 226
Polonium	Carbon 14	Technitium 99
	Tritium	
	Sulfur 35	

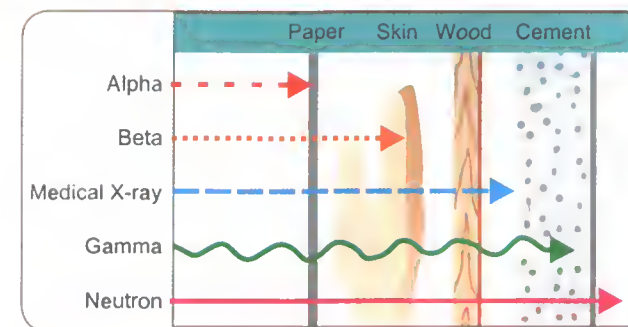
- **Atomic number** is the number of **protons**, and therefore also the total positive charge, in the atomic nucleus.
- **Isotope**: One of two or more atoms that have the **same atomic number** (the same number of protons) but a **different mass number** (i.e. different number of neutrons).
- **Background (natural) radiation** is the ubiquitous ionizing radiation that people on the planet Earth are exposed to, including **natural** and **artificial sources**; it consists of cosmic, terrestrial and internal radiation.
- **Positron** emission involves a particle that has the same mass as an electron but a positive charge. The particle is released from the nucleus when a proton splits into a neutron and positive electron.
- **Wave particle duality**: Short **electromagnetic waves** such as **X-rays** behave **like waves** as well as **particles (photons)**.
- **Radon is a gas** produced by the radioactive decay of the element **radium**.
- **Ionization is more concentrated at the end of particle path**. This is called **Bragg effect**. Used in **proton beam therapy** so that **Bragg peak** can occur within the exact tumor site.
- **C14** is used for **carbon dating**—to estimate the age of organic materials such as wood and bone.

Ionizing and Penetrating Power

- **Ionizing power**: Alpha particle (most dangerous) > Beta particle > Gamma ray
- **Penetrating power**: Gamma rays > Beta particle > Alpha particle (reverse of above!)
- **Penetrating power distances** in tissues: Gamma rays (50 cm) > Beta particles (0.06 - 4 mm) > Alpha particles (0.05 mm).
- **Remember**: Neutrons have the highest penetrating power (more than all the above)
- **Liner energy transfer**: Alpha > Beta > Gamma

Few Extra Points

- **Henry Becquerel** discovered **radioactivity** in 1896.



RADIATION PHYSICS

- There are 3 major ways in which radiation, especially X-ray is absorbed and results in ionization:
 - **Photoelectric effect**: At **low energies** as in **diagnostic radiology** this effect dominates. Here **low energy** incident photons of are completely absorbed by atoms and bound orbital **inner shell electrons** are released as photoelectrons.
 - **Compton effect**: At **higher energies**, as in **therapeutic radiology** this effect dominates; here the **higher energy** incident photon interacts with a **outer shell** 'free electron' (loosely bound electron) and transfers 'some' of the momentum and energy to the electron.
 - **Pair production**: At energy levels **above 1.02 MeV**, the **very high energy** incident photons interact with the electromagnetic field of the **nucleus**.

Some Terms

- **Relative Biologic Effectiveness (RBE)**: The biologic effects produced by a given dose of radiation can be quantified by the RBE value, which relates them to the effects produced by 250 kV photon as a standard. The RBE value will be greater for more densely ionizing radiation, such as neutrons.
- **Linear Energy Transfer (LET)**: This is the amount of ionization occurring per unit length of the radiation track. It is usually expressed in kilovolts per micron, and it increases with the square of the charge of the incident particle. It is thought that low-LET radiation must produce multiple hits on DNA to destroy a cell, whereas high-LET radiation need produce only a single hit on DNA to kill a cell.

CELLULAR EFFECTS OF IONIZING RADIATION

- **Radiobiology** = scientific study of the effects of ionizing radiation on cells and tissues, both normal and malignant.
- The specific target of radiation damage is the **DNA molecule**.

- **DNA damage with double strand breaks** is the apparent **dominant mechanism** of radiation induced cell death.
- Radiation produces **free radical** formation primarily through its ionization of water molecules that may then cause double strand breaks of the DNA.
- Irradiation causes cells to be **arrested** for several hours in the second gap (**G2**) phase of the cell cycle before undergoing mitosis (M phase).
- An important principle to remember is that a **given dose of radiation kills a constant fraction of tumor cells**; hence each repetitive setting achieves a similar reduction of tumor activity.
- **Law of Bergonie** - Radiosensitivity of a cell varies directly with the rate of mitosis and varies indirectly with degree of differentiation
- **Hyperthermia** - Heat is particularly toxic to cells in the relatively radioresistant S phase of the division cycle. Therefore heat and radiation may have additive cytotoxic effect due to their specificity for different parts of the division cycle.

RADIOBIOLOGY

The major factors underlying the different responses of tissues to radiation are often called the

'4 Rs' of Radiobiology

Repair of cellular damage
Re-oxygenation during the course of irradiation
Re-population by tumor cells
Re-distribution of cells in the cell cycle.

- **Repair**
 - Damage to DNA following irradiation is generally **repaired over 6 hours**.
 - However, the degree of repair will vary from tissue to tissue.
 - **Slowly responding tissues** (e.g. connective tissue and spinal cord) have a greater capacity for repair than tumors, as long as the gap between treatment fractions is at least 6 hours, as it is with conventional once daily radiotherapy.
- **Re-oxygenation**
 - The presence of oxygen in tissue is critical for radiation-induced cell kill.
 - Hypoxic tumors are **2-3 times more radioresistant** than well-oxygenated tumor cells.
 - Fractionation of radiation allows tumor re-oxygenation during the course and this allows increased tumor cell kill.
 - Strategies that have been investigated to try to overcome the problem of radioresistant tumor cells are

hyperbaric oxygen or carbogen breathing during radiation therapy, use of hypoxic cell sensitizers such as misonidazole and pimonidazole.

➤ Oxygen administration just before starting radiotherapy is most effective.

• Re-population

➤ Cells proliferate as tumors grow. Additionally they will regenerate during a course of fractionated radiation therapy. This regeneration during treatment is called **re-population**.

➤ Giving radiation therapy in several small doses during the day (multiple daily fractions) may help to overcome tumor repopulation.

➤ Conversely excessive prolongation of radical external beam irradiation over 7-8 weeks may allow significant tumor repopulation.

• Re-distribution

➤ Different parts of the cell cycle are known to have different radiation sensitivities.

➤ The **most radiosensitive phase of the cell cycle to radiation is the Mitotic phase > G2-M phase**.

➤ **Late S phase** is the **most radioresistant phase** of the cell cycle.

• It is anticipated that during a fractionated course of radiotherapy, cells moving through the cell cycle will pass through sensitive phases where they may be more readily eradicated.

• This reassortment or re-distribution favors increased radiation cell kill which is especially true if the cell population has a more rapid turnover time.

Therapeutic Ratio

• Therapeutic ratio for radiation is **a balance between the level of tumor control and the damaging effects on normal tissues**, since all cells in the radiation volume sustain some degree of radiation damage.

• Therapeutic ratio is essential to safe and effective practice of radiotherapy and is the **main criterion** by which any new application of therapeutic radiation to malignant disease should be judged.

Radiation-Derived Units

Quantity	Old unit	SI unit	Name for SI unit
Radioactivity	Curie (Ci)	Disintegrations per second (dps)	Becquerel (Bq)
Radiation Absorbed Dose	RAD	Joule per kilogram (J/kg)	Gray (Gy)

Quantity	Old unit	SI unit	Name for SI unit
Radiation Exposure	Roentgen (R)	Coulomb per kilogram (C/kg)	—
Dose equivalent	rem	Joule per kilogram (J/kg)	Sievert (Sv)

Mnemonics

- Radioactivity: 'Curie and Becky are Active'
- Radiation Absorbed Dose: 'Ra(e)d and Gray' (Colors!)

EXTERNAL BEAM RADIOTHERAPY (EBRT)

- EBRT or **Teletherapy** is the **MC form of radiotherapy**.
- This involves the placement of radioactive source **at a distance (external)** from the patient. The source of radiation is placed **at a distance 5-10 times greater than the depth of tumor to be irradiated (source to skin distance)**. High-energy photons, X-rays or gamma rays are used.
- A **linear accelerator (LINAC)** is MC used to produce **high energy x-rays/electrons** to treat the tumor.

Radioisotope	Half-life	Comment
Cobalt-60	5.3 years	MC used isotope for EBRT; Mean X-ray energy 1.25 MeV
I131	8.1 days	Used for treating hyperthyroidism and thyroid cancers ; beta and gamma emitter
Phosphorus-32	14.5 days	Used in treating polycythemia ; beta emitter

Fractionation

- Conventional external beam radiation therapy is usually delivered in 'fractionated' course using daily doses of 2 Gy per fraction with a **minimum 6 hours interval** between each sitting. After each dose the same proportion of 'sensitive' cells in particular phases of the cell cycle are killed. Each dose of 2 Gy roughly reduces the tumor population by 50%. Fractionation exploits the different responses of rapidly dividing tumors and late responding normal tissues to ionizing radiations.
- **Hypofractionation**: Total dose of radiation is divided into large doses and treatments are given **once a day or less often**. It is given over a shorter period of time (fewer days or weeks) than standard radiation therapy. Hypofractionation is routinely used for **palliation**; also used in tumors with low alpha/beta ratio - **malignant melanoma, breast, prostate** cancers.
- **Hyperfractionation**: Total dose of radiation or chemotherapy is divided into small doses and treatments are given **more than once in a single day**.

EXTRA EDGE

- **Prophylactic cranial irradiation** is a technique used to combat the occurrence of metastasis to the brain in highly aggressive cancers that commonly metastasize to brain, most notably **small-cell lung cancer**, also used in **acute lymphoid leukemia**.

Radiation Schedules

- **Palliative radiation programs** use **300 cGy** per fraction for 10 fractions (total 3000 cGy) to **shrink the tumor and relieve symptoms quickly since patients lifespan is less**. (higher radiation dose for shorter time).
- **Curative radiation programs** are delivered once a day, 5 days a week in **150-200 cGy** fractions over **5-7 weeks**. (lower radiation dose for longer time).
- **Total radiation dose** for **curative radiotherapy** range from **4500 to 8000 cGy**.
- For squamous cell Ca of head and neck, **6500-7000 cGy** is used.

BRACHYTHERAPY

- A form of radiation therapy in which the **source is placed close to the tumor** (interstitial or intracavitary).
- The device used for brachytherapy is first introduced into the patient and its position checked with radiographs. The radioactive sources are later introduced into the device by '**after-loading**' technique. Such a method reduces radiation exposure to the personnel treating the patient.
- **Isotopes used in brachytherapy** are as follows:

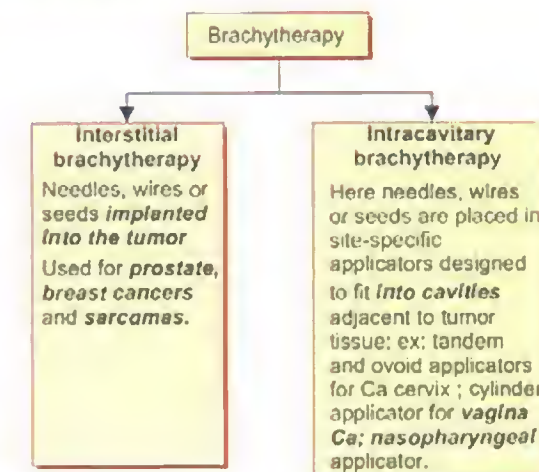
Radium-226	1600 years	Was the first isotope used BUT is obsolete now due to radon gas emission into bone and very high cost of extraction.
Uranium	4.5 billion years	Decays into thorium and radium
Iridium-92	74 days	MC used for High dose rate (HDR) brachytherapy; Mean X-ray energy 0.37 MeV
Caesium 137	30 years	MC used for Low dose rate (LDR) brachytherapy; Mean X-ray energy 0.66 MeV

EXTRA EDGE

Other radioisotopes used in brachytherapy are: Cobalt-60, Strontium 90, Tantalum 182, Yttrium 90, Samarium-145

- High Dose Rate (HDR) brachytherapy > **12 Gy/hr**, Medium Dose Rate (MDR) **2-12 Gy/hr** and Low Dose Rate (LDR) **0.4-2 Gy/hr** at the **point of dose calculation**.
- **Permanent implant seed brachytherapy**: A radioisotope is implanted permanently into the tumor site, emitting low dose of radiation over the lifetime of its radioactivity. **Iodine-125I, Palladium-103Pd and Gold-199Au** are used.

Types of Brachytherapy



Manchester System

- The Manchester system was designed for use with LDR radium **brachytherapy of Ca cervix**. It is the most commonly used technique. It was published in 1938 by **Tod and Meredith** and remains in use today. Refinement of the method occurred in the 1950s. Most centers use a tandem (long tube that is inserted into the uterine cavity) and two ovoids/colpoplasts that lie laterally to the tandem.
- **Point A** - Representing the **paracervical triangle (where uterine artery crosses the ureter)**. Point A is defined as 2 cm above the lateral vaginal fornices and 2 cm lateral to the central uterine tube.
- **Point B** - Representing the pelvic side wall/**obturator nodes**, Point B is located 5 cm lateral to midline at the same level as point A. It also gives a guide as to the lateral spread of the radiation dose.

3D CRT

- **3D CRT = Three-dimensional-Conformal Radiation Therapy**.
- 3D images radiotherapy using images from CT scan and MRI to plan precise fields of radiation to the patient's tumor—allows coverage of the diseased cells while keeping radiation away from nearby normal organs, such as the eyes.
- Conformal means that the target volume is very well defined or shaped to the tumor.
- **Stereotactic radiosurgery (SRS)** is a form of 3D CRT of **brain or spine**.
- **Stereotactic body radiation therapy (SBRT)** refers to one or several stereotactic radiation treatments with the body, **excluding the brain or spine**.
- Both the above are delivered by a team involving a radiation oncologist, neurosurgeon and radiotherapist.

Conditions Treated with Stereotactic Radiation

Stereotactic radiosurgery (SRS)	Stereotactic body radiation therapy (SBRT)
Conditions involving the brain or spine including: <ul style="list-style-type: none">▪ Malignant gliomas and other primary brain tumors▪ Brain metastases▪ Meningiomas▪ Acoustic neuromas▪ Brain AV malformations▪ Trigeminal neuralgia▪ Uveal melanoma▪ Epilepsy▪ Glomus tumor	To treat small tumors in the chest, abdomen or pelvis that cannot be removed surgically or treated with conventional radiation therapy, including: <ul style="list-style-type: none">▪ Small lung cancers (< 5 cm)▪ Lung and liver metastases

Other Names for Stereotactic Radiosurgery

- Stereotactic radiation may be delivered by a number of different devices; *brand name* stereotactic treatment machines include: *Axesse, CyberKnife, Gamma Knife, Novalis, Primatom, Synergy, X-Knife, TomoTherapy or Trilogy.*
- Gamma knife uses **cobalt** as radiation source; Co-60 is a **naturally occurring isotope.**

Gamma knife radiosurgery	Cyberknife
Rigid stereotactic frame used	Mask or fiducials used
Robotic positioning of head in a collimator helmet	Robotic positioning of LINAC (LINear ACcelerator which produces high energy x-rays) around the patient
Used only for intracranial lesions	Useful for intracranial and body lesions (including spinal cord and lung)
Single day procedure	Multiple day procedure

ADVERSE EFFECTS OF RADIATION

Stochastic Effects

- These effects have **no threshold** and the severity of the effect **does not vary with the dose.** The **probability of occurrence**, however, **increases as the dose increases.**
- Examples are **cancers** (particularly, leukemia that has a latent period of 2 to 10 years post-exposure). There is a **longer latent period for solid tumors (10 to 40 years)** such as **squamous cell carcinoma of the skin and adenocarcinoma of the breast or lung.** Genetic effects are also considered under this category.
- Irradiation of whole body is **fatal** if single exposure is above **400 Rads.**

Non-stochastic Effects (Deterministic Effects)

- The severity of the effect is **proportional to the dose** and the effects are *not seen below a certain threshold level* of radiation.
- **Cataracts** (a minimum dose of 200 rem (2 Sv) is required for the development of cataracts); **Sterility; erythema; radiation myelitis** and vessel damage come under this category.

Potential Effects of In Utero Exposure

- **Prenatal death** occurs if the radiation is received during perimplantation.
- The **most sensitive period for congenital abnormalities** is during the *period of organogenesis.*
- The **most sensitive period for neonatal death** to occur following radiation exposure is between *3 and 5 weeks gestation.*
- **Mental retardation:** *MC documented abnormality in humans who are prenatally exposed to radiation.* The fetus is most susceptible to radiation delivered during the 8 to 15 week period.
- Growth retardation, sterility, induction of malignancies (leukemia), and neurological impairment.

Acute Radiation Sickness (ARS)

This refers to the effects of a whole body dose radiation (100 rad or more), usually over a short period of time (few minutes). ARS syndromes include:

- **Hematopoietic** syndrome: Due to bone marrow suppression; 2 Gy.
- **GI** syndrome: Nausea and vomiting, diarrhea and cramping pain. 10 Gy.
- **CNS:** Deteriorating consciousness, respiratory depression, and increased vascular permeability; 20 Gy.

Subacute and Long-term Effects of Radiotherapy

- **CNS:** Lhermitte's sign, infarction, necrosis, transverse myelitis (presents after 1 year), leukoencephalopathy.
- **Skin:** **Erythema**, dry and moist desquamation, hyperpigmentation of irradiated skin.
- **Heart:** **Asymptomatic pericardial effusion** (MC). It is usually detected by chest X-ray and confirmed by an echocardiogram. Chronic cardiac changes include a pancarditis due to peri/endo/myocardial fibrosis – detected by *endomyocardial biopsy.*
- **Lung:** Early and late radiation pneumonitis.
- **Digestive tract:** Chronic radiation enteropathy: diarrhea, cramping, obstruction, progressive **bowel fibrosis**, perforation, fistula formation and stenosis.
- **Bladder:** Increased frequency of urination, dysuria, **obstructive uropathy.** Mucosal desquamation and ulceration may occur. Late effects include telangiectasias, fibrosis and ulceration.

- **Testis and ovaries:** Type B spermatogonia are exquisitely sensitive to the effects of radiation, amenorrhea and sterility.
- Bones: Prone to **fractures.**

RADIOSENSITIVITY

	Most radiosensitive	Least radiosensitive
Tissue	Bone marrow	Nervous tissue
Blood cell	Lymphocyte	Platelet
Stage of cell cycle	G2-M interphase (mitosis or G2-M phase)	S phase
Cell type	Rapidly dividing (vegetative intermitotic cells)	Quiescent (fixed postmitotic cells)
Ocular structure	Lens	Sclera
Layer of retina	Rods (more than cones)	Ganglion cell layer

Radiosensitivity of Tumors

Highly radiosensitive tumors	Poorly radiosensitive tumors
<ul style="list-style-type: none">▪ Seminoma testis▪ Dysgerminoma ovary▪ Ewing's sarcoma▪ Limited-stage Hodgkin's lymphoma▪ Some non-Hodgkin's lymphomas▪ Neuroblastoma▪ Small cell lung cancer▪ Ca cervix and uterus, vagina▪ Head and neck Ca (larynx, pharynx, esophagus, oral cavity)▪ Spinal metastases from multiple myeloma	<ul style="list-style-type: none">▪ Malignant melanoma▪ Glioma▪ Sarcomas (osteo, fibro, liposarcomas)▪ Ca colon▪ Ca kidney▪ Ca pancreas▪ Metastases from any of the above

Radiosensitizers and Radioprotective agents

Radiosensitizers	Radioprotective agents
<ul style="list-style-type: none">▪ Hypoxic cell sensitizers: etanidazole, misonidazole, metronidazole, nimorazole, efaproxiral▪ Non Hypoxic cell sensitizers: bromodeoxyuridine, iododeoxyuridine▪ Chemotherapy agents: hydroxyurea, cisplatin, carboplatin, 5-FU, paclitaxel, gemcitabine, bleomycin, mitomycin, dactinomycin, doxorubicin▪ Molecular targeted agents: cetuximab, gefitinib, farnesyl transferase inhibitors	<ul style="list-style-type: none">▪ Amifostine▪ Etramustine▪ Pentoxifylline▪ Zinc oxide▪ G-CSF and GM-CSF (colony stimulating factor)

Tolerance of Various Organs to Radiation

Organ	Dose
Testis	2 Gy
Ovary	8 Gy
Eye	9 Gy
Lung, Kidney	25 Gy
Liver	40 Gy
Brain	60 Gy

Radiolabelled Antibodies

These deliver high levels of radiation locally to the tumor bed, thereby avoiding systemic toxicity.

Drug	Labeled with	Used for Rx
Ibritumomab tiuxetan (anti-CD20)	Y-90	Low-grade NHL
Tositumomab (anti-CD20)	I-131	Low-grade NHL

NEWER TOPICS

VMAT (Volumetric Modulated Arc Therapy)

- **VMAT** delivers a **precisely sculpted 3D dose distribution with a single 360-degree rotation of the linear accelerator gantry.**
- VMAT therapy differs from existing techniques like helical IMRT or intensity-modulated arc therapy (IMAT) because it **delivers dose to the whole volume**, rather than slice by slice.

Intraoperative Radiotherapy

- In intraoperative radiation therapy (IORT), by using **low energy x-rays or electron beams** the intraoperative radiation can be given with a high dose, local and precisely into the tumor or directly after resection to the **tumor bed.** This minimizes collateral tissue damage also reduces side effects.
- Used in **breast Ca, Ca skin, spinal metastases and colorectal Ca.**

IMRT (Intensity Modulated Radiation Therapy)

- IMRT differs from 3D-CRT by modifying the intensity of the radiation within each of the radiation beams and lesser radiation exposure to normal tissues.
- Improved outcomes have been shown for **prostate cancer** patients receiving IMRT.

PREVENTIVE AND SOCIAL MEDICINE (PSM) ASPECTS OF RADIATION

- Man receives about *50 mrad/year* from *terrestrial radiation*.
- *Kerala* contains uranium deposits where exposure can be as high as *2000 mrad/year*.
- *Atmospheric radiation* exposure = *2 mrad/year*.
- *Internal radiation* exposure (from radioactive matter stored in body tissues) = *25 mrad/year*.
- Total natural radiation that man is exposed to = *0.1 rad/year*.

Maximum Permissible Radiation Exposure

- National Council on Radiation Protection guidelines for maximum permissible dose (MPD) is given as follows:

General public, Annual MPD	1 mSv (0.1 rem)
Radiation workers, Annual MPD	50 mSv (5 rem)
Radiation workers, cumulative MPD	10 mSv x Age
MPD during pregnancy	5 mSv (0.5 rad, 0.5 rem)

CHAPTER

32

Nuclear Medicine

RADIONUCLIDE IMAGING-BASIC PRINCIPLES

Nuclear (or radionuclide) imaging requires intravenous administration of radiopharmaceuticals (isotopes or tracers). Once injected, the isotope traces physiologic processes and undergoes uptake in specific organs. During this process, radiation is emitted in the form of photons, generally gamma rays, generated during radioactive decay when the nucleus of an isotope changes from one energy level to a lower one.

- Sensitive devices which detect the radioactivity are the *Geiger-Muller counter* (not used routinely now) and the *scintillation counter*.
- The gamma rays emitted by the isotopes are detected by a *gamma camera* enabling an image to be produced. A gamma camera consists of a *circular sodium iodide scintillation crystal* (the primary radiation detection element), usually 40 cm in diameter coupled to a number of photomultiplier tubes.
- The procedures routinely performed in nuclear medicine departments can be broken down into four main categories: *imaging procedures; in vivo function studies; in vitro tests and therapeutic applications*.
- The *ideal radionuclide* for imaging using a *standard gamma camera* will be:
 - a. A high abundancy monoenergetic gamma emitter of energy 75-300 keV
 - b. It will decay with a half-life similar to the length of investigation by isomeric transition or electron capture
 - c. Have low internal conversion and
 - d. No radioactive daughter products.
- The radionuclide MC used is *Technetium-99m (^{99m}Tc)*. The prefix '*m*' - denotes 'metastable' state of technetium 99. It is readily prepared, has a convenient *half-life of 6 hours* and emits gamma radiation of suitable energy for easy detection.

Radioisotope Half Lives

Radionuclide	Half Life
Carbon-11 (¹¹ C)	20 minutes
Technetium-99m (^{99m} Tc)	6 hours
Iodine-123 (¹²³ I)	13 hours
Iodine-131 (¹³¹ I)	8 days
Indium-111 (¹¹¹ In)	68 hours
Thallium-201 (²⁰¹ Tl)	73 hours
Gallium-67 (⁶⁷ Ga)	78 hours
Strontium-90	28 years
Carbon-14 (¹⁴ C)	5600 years

EXTRA EDGE

- **Memory aid:** To remember half life of I-123 and I-131—Remember the extra number **138**, i.e. 13 hours and 8 days (and of course remember that hours comes before days!).

COMMONLY USED RADIONUCLIDE SCANS

Bone Scan

- *Technetium-99m (^{99m}Tc)* is MC used; also Fluoride-18 (F18) is used.
- **HOT spots:** Due to increased uptake of the radionuclide corresponding with *increased blood flow or increased osteogenic activity*—seen in *osteomyelitis, healing fracture, arthritis, Paget's disease, primary or metastatic malignancy*.
- **COLD spots:** Due to decreased uptake of radionuclide corresponding with *no osteogenic activity and decreased blood flow or bone destruction (purely lytic lesions)* - seen in *avascular necrosis, multiple myeloma*.

Renal Scan

- *Iodine-131 (¹³¹I) Hippuran*. Evaluation of *function* in renal insufficiency; visualization is poor, radiation dose can be high.

- **Technetium-99m (^{99m}Tc) DMSA** (dimercaptosuccinic acid). **Renal cortical imaging** only; **renal size, shape, renal scarring** (in recurrent UTI) and position noted.
- **Technetium-99m (^{99m}Tc) DTPA** (diethylene triamine pentaacetic acid). **Estimation of GFR, vesicoureteric reflux, renal tract obstruction.**
- **Technetium-99m (^{99m}Tc) mercaptoacetyl triglycine (MAG3).** For assessing **function of renal tubules, collecting ducts and renal blood flow.** Imaging of the renal parenchyma **within minutes of injection** and **with low radiation** dose. **Best agent in moderate to severe renal failure.**

Cardiac Scan

- **Myocardial perfusion scintigraphy:** Test for **reversible ischemia: Thallium-201 (²⁰¹Tl)** or **Technetium-99 sestamibi** or **tetrofosmin scan:** **Normal myocardium**

appears hot and ischemic or infarcted areas appear cold; reversible ischemia indicated by 'cold spot' that returns to normal after 4 hours of rest.

- **Technetium-99m (^{99m}Tc) stannous pyrophosphate scan.** Recently damaged myocardium (**acute MI**) seen as **hotspot**; test is positive only 18 hours post infarction.
- **Technetium-99m (^{99m}Tc) labeled ventriculogram.** ^{99m}Tc labeled serum albumin or RBCs are used. Shows regional abnormal wall motion.
- **MUGA (multiple-gated blood pool acquisition) scan,** again using ^{99m}Tc labeled serum albumin or RBCs: **Most accurate method for measuring cardiac ventricular ejection fraction;** also used for monitoring **anthracycline cardiotoxicity.**
- **18-FDG PET** has become the **gold standard non-invasive test** to **evaluate myocardial viability.**

Adrenal scan	For localization of pheochromocytoma when CT or MRI findings are equivocal, Iodine 123 or 131 labeled MIBG (metaiodobenzylguanidine) is used
Bleeding scan	Detection of source of GI bleeding <ul style="list-style-type: none">• Technetium-99m (^{99m}Tc) sulfur colloid scan• Technetium-99m (^{99m}Tc) red cell scan – superior for localizing <i>intermittent bleeding</i>
Bone scan	<ul style="list-style-type: none">• Metastatic markings (Ca likely to go to bone—breast, prostate, kidney, thyroid, lung)• Evaluation of delayed union of fractures, osteomyelitis, avascular necrosis of femoral head, evaluation for hip prosthesis• Differentiation of traumatic and pathologic fractures
Brain scan	<ul style="list-style-type: none">• Metastatic workup• Determination of blood flow in brain death or atherosclerotic disease)• Evaluation of space occupying lesions (tumor, hematoma, abscess, AV malformation)• Encephalitis
Cancer scan	• Technetium-99m (^{99m}Tc) + arcitumamab, CEA-Scan. For imaging of cancers with increased levels of CEA and has been found to be more sensitive and specific than CT scans in the detection of both resectable and nonresectable disease
Gallium scan	• Location of abscesses and chronic inflammatory lesions, infections (osteomyelitis); fever of unknown origin, lymphoma, staging and follow-up for disease detection, diagnosis of lung cancer, melanoma and other neoplasms
Hepatobiliary scan (HIDA or, DISIDA, BRIDA scan)	<ul style="list-style-type: none">• DISIDA (Di-isopropyl iminoacetic acid); HIDA (hepatobiliary iminoacetic acid); BRIDA (mebrofenin)• Differential diagnosis of biliary obstruction, acute cholecystitis, biliary atresia; not good for biliary stones• Cases of biliary atresia typically demonstrate relatively good hepatic uptake with no evidence of excretion into the bowel at 24 hours, unless cystic duct is completely occluded and cholecystitis is present• Pretreatment with phenobarbital (5 mg/kg/day for 5 days) to increase biliary secretion by stimulating hepatic enzymes is frequently helpful to minimize the possibility of a false-positive study in a patient with a patent biliary system but poor excretion• Non-visualization of gallbladder on hepatic scintigraphy is suggestive of acute calculous cholecystitis (i.e. cholecystitis due to gallstones).
Indium-111 (¹¹¹In) Octreotide scan	• Imaging of tumors with somatostatin receptors (gastrinoma, insulinoma, pheochromocytoma, small cell lung cancer)

Contd...

Contd...

Iodine-125 (¹²⁵I) Fibrinogen scanning	• Detection of venous thrombosis in the lower extremities. Patient is scanned several hours and several days after injection of tracer. Identification of clots at or below knees. False positives with varicosities, cellulitis, incisions, arthritis and hematomas. Tracer availability problem
Lungs scan (V/Q scan)	• Evaluation of pulmonary embolism
Strantium-89 (⁸⁹Sr) Metastran	• Palliative therapy for multiple painful bony metastases (prostate or breast cancer). Because agent is a pure beta emitter, radioactivity remains in the body, so no special precautions are needed
Thyroid scan	• Technetium-99m (^{99m}Tc) pertechnate. Evaluation of nodules. Scan patterns in conjunction with lab test may help in diagnosing hyperfunctioning adenoma. Plummer and Grave's disease, multinodular goiter, localization of ectopic thyroid tissues (especially after thyroidectomy for cancer), identification of superior mediastinal masses
Scrotal scan	• To differentiate testicular torsion from other causes of testicular swelling
Pancreas scan	• Selenium 75-Selenomethionine imaging
Hepatobiliary scan (HIDA.....)	• Non-visualization of gallbladder on hepatic scintigraphy is suggestive of acute calculous cholecystitis (i.e. cholecystitis due to gallstones)

Other technetium-99m scans

- Gold standard for diagnosis of **malignant otitis externa (Pseudomonas)** is a **Technetium 99 bone scan.**
- Radionuclide scanning procedures using **technetium (Tc) 99m sulfur colloid, gallium (Ga) 67 citrate, or indium (In) 111-labeled WBCs** may be useful in identifying and/or localizing inflammatory processes such as **abscess.**
- A **Meckels' diverticulum** may be demonstrated by IV injection of **99mTc**, which localizes in the **ectopic gastric mucosa - Meckel scan.**
- **Tc99m labeled WBCs** are also taken by areas of *noninfectious inflammation* (e.g. **inflammatory bowel disease**).
- **Tc99m labeled RBCs** are used for assessing ventricular function; for detecting GI bleeds and for imaging liver hemangiomas.
- **Kupffer cells** of the liver take up **Tc99m sulfur colloid** very well—'Phagocyte scan'.
- Technetium-99m (^{99m}Tc)—labelled **sestamibi** (MIBI) isotope scans identify 75% of **abnormal parathyroid glands.**

More High Yield Point One-Liners

- **I-131** has a **half life** of **8 days.**

- **Somatostatin Receptor Scintigraphy** is the initial imaging modality of choice for localizing both the **primary and metastatic NETs.**
- For ventilation scans, macroaggregates of albumin labelled with ^{99m}Tc are used. For perfusion scans the patient inhales a radioactive gas such as xenon-133, xenon-127 or krypton-81m. Aerosols labelled with ^{99m}Tc may be used instead of gases.
- **Salivary gland scanning** with ^{99m}Tc gives **hot scan** in **Warthin's tumor (adenolymphoma).**
- A **NeutroSpec scan** is used for identifying deep seated chest or abdominal infections.
- 90Y-radiolabelled **ibritumomab tiuxetan**, for the treatment of adult patients with rituximab-relapsed or -refractory **CD20+ follicular B-cell NHL.**
- **Potassium-40** is a naturally occurring radioactive isotope within the human body.
- **Strontium** may be used as supplement for **osteoporosis** much like calcium, however the two should be taken at different times since strontium **competes with calcium for absorption in intestine.**
- **Strontium 89** and **samarium 153** are two radionuclides that are preferentially taken up in bone, particularly sites of **new bone formation** - used in **treatment of bony metastases** (**8 Gy** in single dose).

Hot Images !



Fig. 33.1: Case of Hansen's disease—BT with patch on ear and enlarged greater auricular nerve (Courtesy: Dr Akshi)

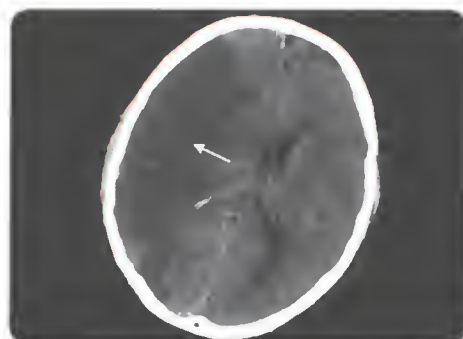


Fig. 33.2: Axial section of computed tomography scan showing right ischemic stroke (arrow).



Fig. 33.3: Coronal section of computed tomography scan showing hyperdense area within sulcus—subarachnoid hemorrhage (arrow)

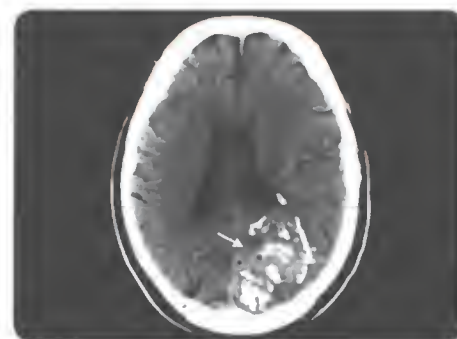


Fig. 33.4: Axial section of computed tomography scan showing left occipital arteriovenous malformation (AVM) (arrow)

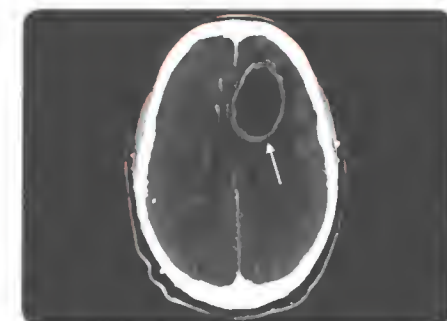


Fig. 33.5: Axial section of computed tomography scan showing brain abscesses involving the left parietal region (arrow)

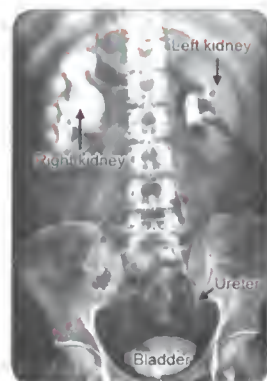


Fig. 33.6: Intravenous pyelography (IVP) of kidneys, ureters and urinary bladder showing hydronephrosis on right side

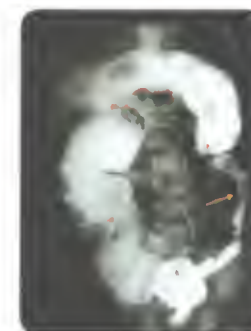


Fig. 33.7: Barium enema radiograph showing aganglionic segment (yellow arrow) and megacolon (green arrow) in Hirschsprung's disease

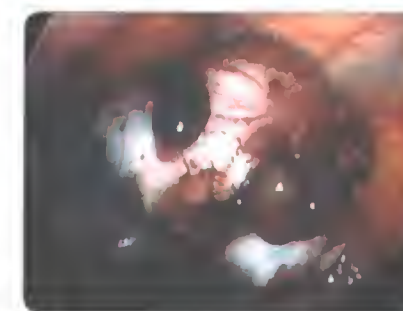


Fig. 33.8: Deposits of endometrial tissue on the surface of ovary forming chocolate cysts in the ovary



Fig. 33.9: Showing hydrocele (swelling of scrotum) in a patient

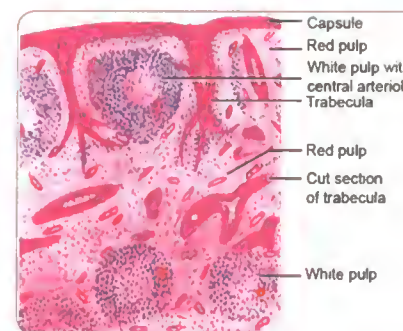


Fig. 33.10: Microscopic structure of spleen

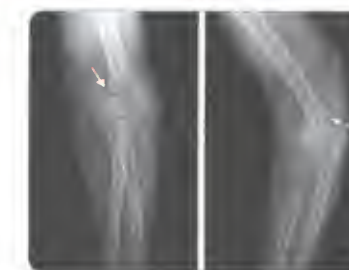


Fig. 33.11: Radiographs showing supracondylar fracture of the shaft of humerus in AP and lateral views (arrows showing)

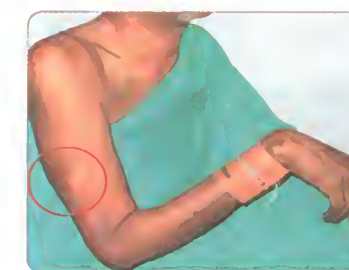
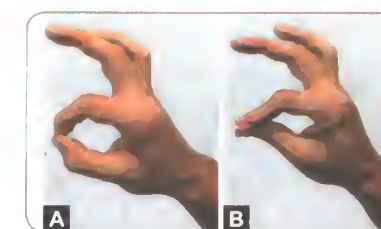


Fig. 33.12: Wrist drop deformity in a patient showing swelling in posterior aspect of arm due to pathology of radial nerve (Red circle)



Figs. 33.13A and B: A. OK sign (by pinching thumb and index finger together). Positive OK sign indicates integrity of anterior interosseous nerve which supplies flexor pollicis longus and lateral half of flexor digitorum profundus; B. Triangular sign indicates inability to flex the distal phalanx hence the distal phalanges of thumb and index finger are approximated to each other so that OK sign (a circle) is changed in to a triangle suggesting injury to anterior interosseous nerve

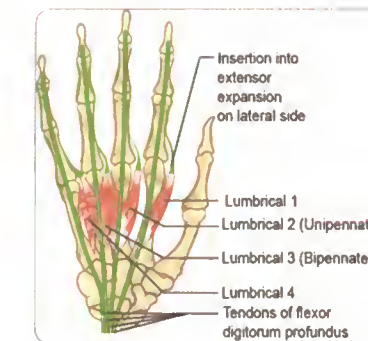


Fig. 33.14: Origin and insertion of adductor pollicis muscle

Hot Images !



Fig. 33.1: Case of Hansen's disease—BT with patch on ear and enlarged greater auricular nerve (Courtesy: Dr Akshi)

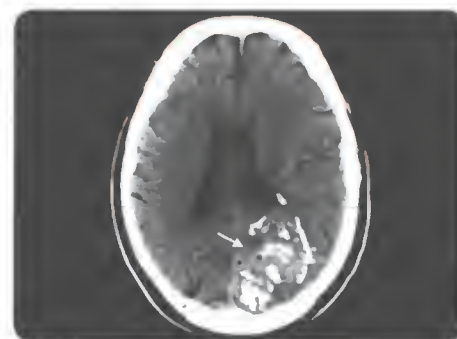


Fig. 33.4: Axial section of computed tomography scan showing left occipital arteriovenous malformation (AVM) (arrow)

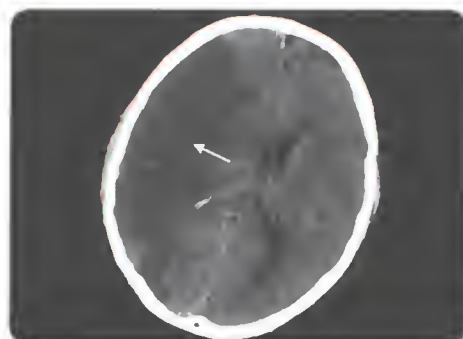


Fig. 33.2: Axial section of computed tomography scan showing right ischemic stroke (arrow).



Fig. 33.3: Coronal section of computed tomography scan showing hyperdense area within sulcus—subarachnoid hemorrhage (arrow)

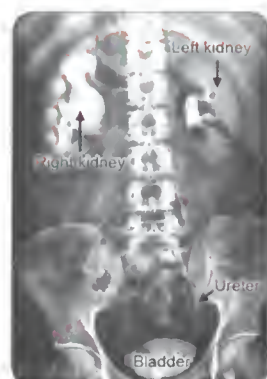


Fig. 33.6: Intravenous pyelography (IVP) of kidneys, ureters and urinary bladder showing hydronephrosis on right side



Fig. 33.7: Barium enema radiograph showing aganglionic segment (yellow arrow) and megacolon (green arrow) in Hirschsprung's disease

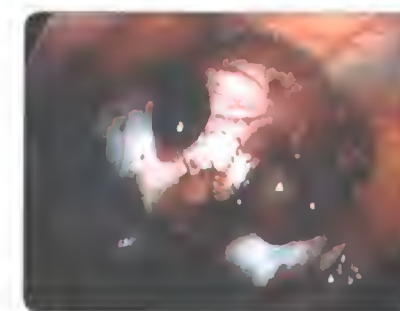


Fig. 33.8: Deposits of endometrial tissue on the surface of ovary forming chocolate cysts in the ovary



Fig. 33.9: Showing hydrocele (swelling of scrotum) in a patient

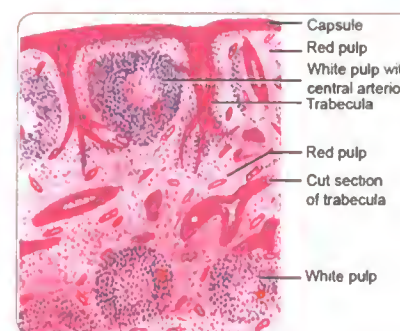


Fig. 33.10: Microscopic structure of spleen

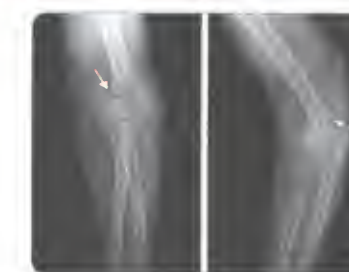


Fig. 33.11: Radiographs showing supracondylar fracture of the shaft of humerus in AP and lateral views (arrows showing)

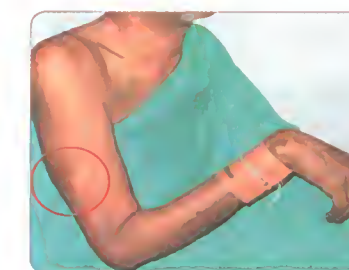
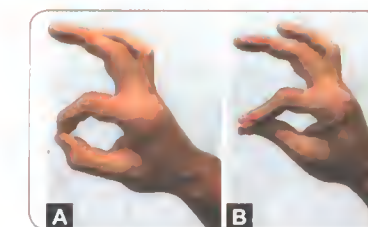


Fig. 33.12: Wrist drop deformity in a patient showing swelling in the posterior aspect of the arm due to pathology of the radial nerve (Red circle)



Figs. 33.13A and B: A. OK sign (by pinching thumb and index finger together). Positive OK sign indicates integrity of anterior interosseous nerve which supplies flexor pollicis longus and lateral half of flexor digitorum profundus; B. Triangular sign indicates inability to flex the distal phalanx hence the distal phalanges of thumb and index finger are approximated to each other so that OK sign (a circle) is changed into a triangle suggesting injury to anterior interosseous nerve

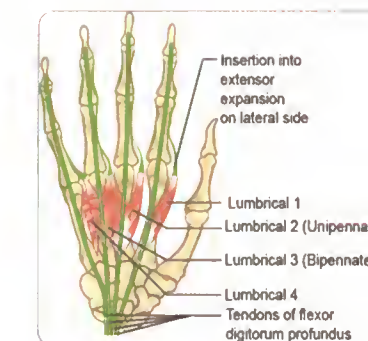


Fig. 33.14: Origin and insertion of adductor pollicis muscle

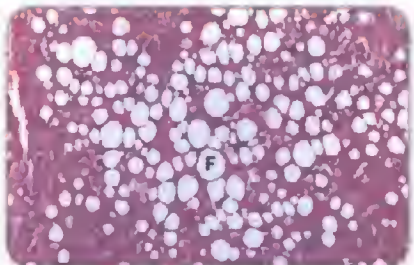


Fig. 33.28: Steatosis. Steatosis or fatty change is characterized by replacement of the hepatocyte cytoplasm with fat droplets (F).

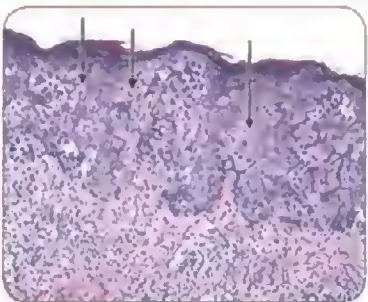
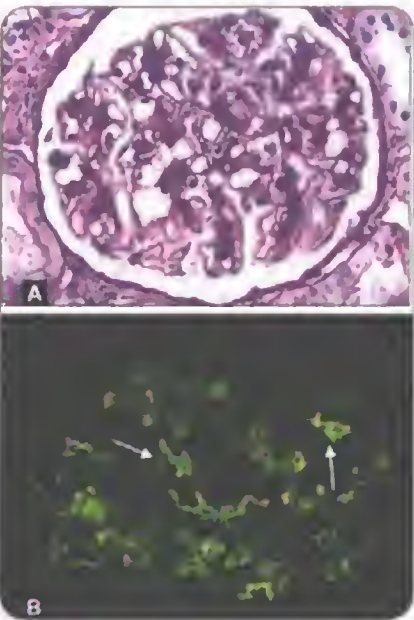
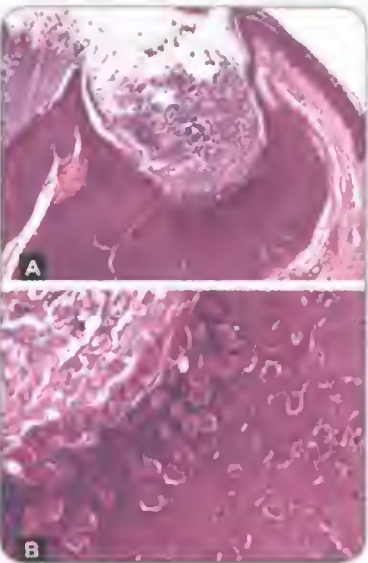


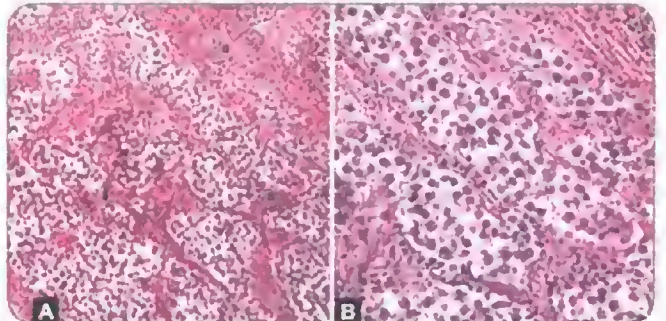
Fig. 33.31: Paget's disease of the nipple. The epidermis contains large tumor cells with abundant pale cytoplasm (arrows).



Figs. 33.29A and B: IgA nephropathy A. The glomerulus shows widening of mesangial areas which contain an increased number of mesangial cells. B. Immunofluorescence microscopy shows deposits of IgA in the mesangial areas (arrows).



Figs. 33.32A and B: Molluscum contagiosum A. Infection by this poxvirus produces an umbilicated dell in the epidermis. Molluscum bodies are most numerous in the granular and cornifying layers. B. Molluscum bodies are cytoplasmic eosinophilic bodies that are divided into small packets by septa and squeeze the nucleus to one side of the cell.



Figs. 33.30A and B: Seminoma A. The tumor is composed of clear cells arranged in groups surrounded by fibrous septa (S) infiltrated with lymphocytes. B. At higher magnification the tumor cells have centrally located vesicular nuclei surrounded by clear cytoplasm and distinct plasma membranes.

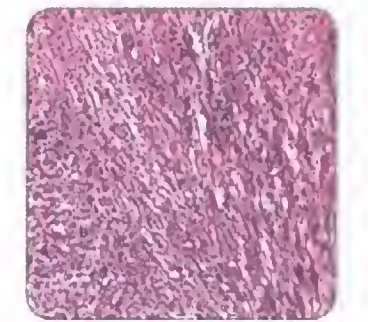


Fig. 33.33: Schwannoma. Tumor is composed of spindle cells resembling normal neural sheath cells. In one area the cells are arranged into dense bundles (Antoni A area), whereas in the other they are loosely structured (Antoni B).



Fig. 33.34: Red cells (RBCs) casts in the urine. Note the red cells aggregation as a cast of the tubule

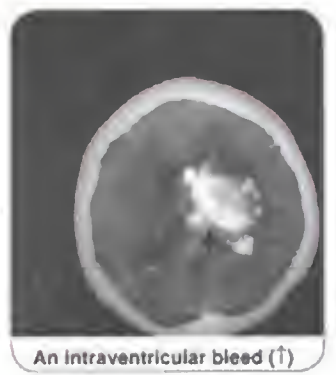
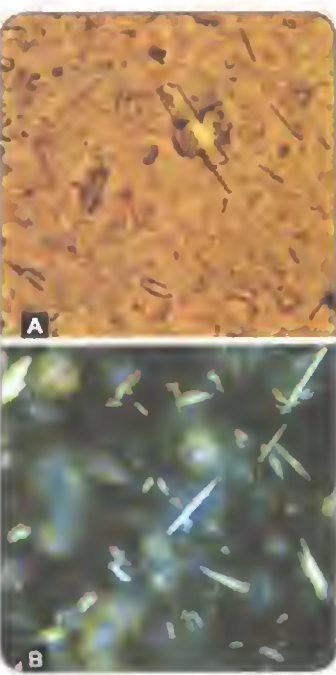


Fig. 33.35: CT scan in different CNS disorders



Figs. 33.36A and B: Synovial fluid examination by polarised light microscopy; A. Crystals of calcium pyrophosphate, which tend to be rather brick-shaped; B. Needle-shaped crystals of uric acid. They react with nitric acid and ammonium hydroxide to give a purple colour (murexide test)



Fig. 33.37: Capillary naevus (naevus flammeus). Note the salmon—coloured patch on the left side of the face



Fig. 33.38: Carbuncle in the nape of the neck—typical site. Note the wide area of involvement and dark area—charcoal like Ash-grey slough is specific.



Fig. 33.39: External angular dermoid, right sided.



Fig. 33.40: Strawberry scrotum—multiple sebaceous cysts on the scrotum.

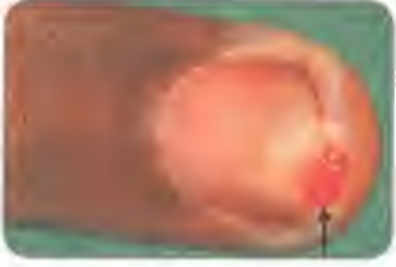


Fig. 33.41: Glomus tumour in finger tip—subungual region.



Fig. 33.42: Glomus tumour in finger tip—subungual region.

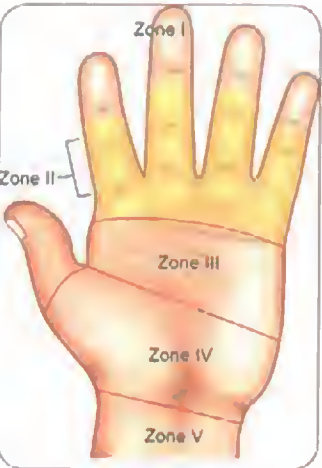


Fig. 33.43: Glomus tumour in finger tip—subungual region.



Fig. 33.44: Glomus tumour in finger tip—subungual region.



Fig. 33.45: Glomus tumour in finger tip—subungual region.



Fig. 33.46: Glomus tumour in finger tip—subungual region.



Fig. 33.47: Glomus tumour in finger tip—subungual region.

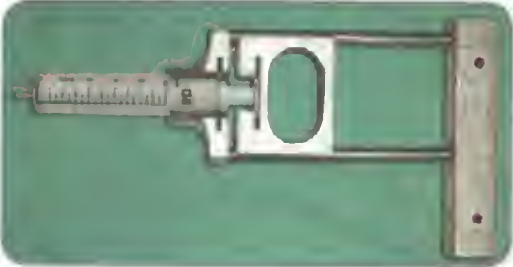


Fig. 33.48: FNAC vacuum creator with loaded syringe (FNAC gun; Cameco syringe (Sweden) holder). (Courtesy: Dr Krishna Upadhy, MD, Nandikoor Laboratory, Mangaluru)



Fig. 33.49: Thyroglossal cyst in a boy. It is a midline swelling with a 'TUG' feeling while protruding the tongue out.



Fig. 33.50: Peau d'orange appearance of skin.

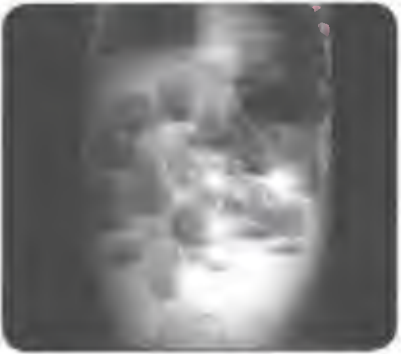
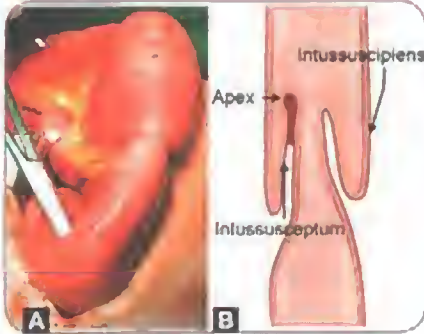
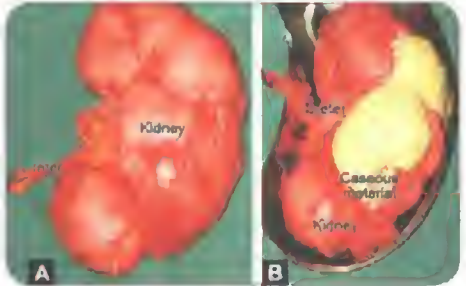


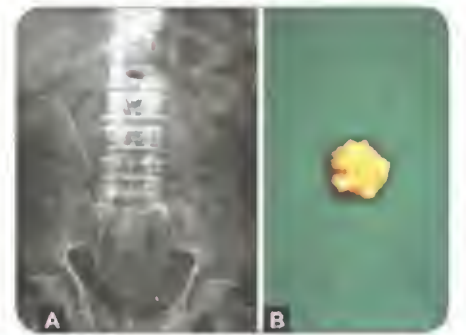
Fig. 33.51: Plain X-ray abdomen showing multiple air fluid levels due to bowel obstruction.



Figs. 33.52A and B: A. Typical intussusception—on table look; B. Parts of intussusception.



Figs. 33.53A and B: Specimen of kidney showing dilatation and caseous material as content. It is tuberculous pyonephrosis. Ureter is visualised in the specimen. Often there may be ureteric stricture due to tuberculosis.



Figs. 33.54A and B: (A) 'J' stent right side—used after UrS (ureterorenoscopy) in ureteric stone extraction; (B) removed ureteric stone.



Fig. 33.55: Child showing extrophy bladder.



Fig. 33.56: Specimen of testicular tumour. Note the cystic and solid areas of teratoma

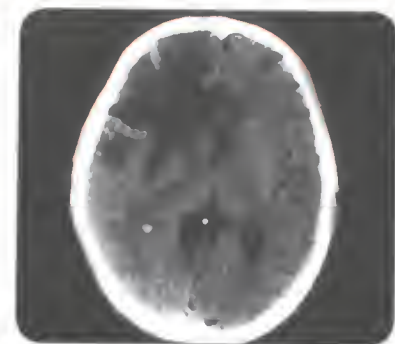


Fig. 33.57: CT scan showing intracerebral brain haemorrhage.

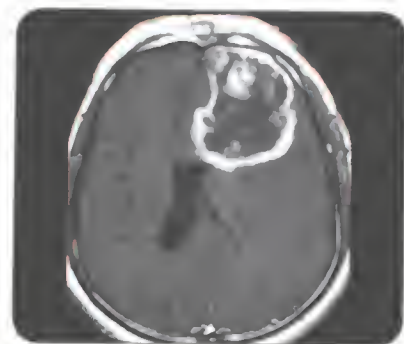


Fig. 33.58: MRI brain showing glioblastoma multiforme. It is very aggressive malignant tumour.



Figs. 33.59A and B: Acromegaly due to pituitary tumours. Note the operated scar in the frontal region.

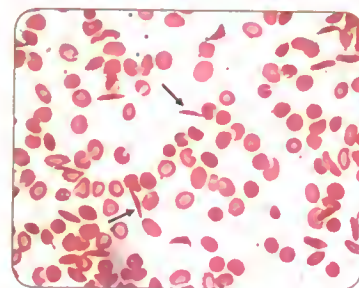


Fig. 33.60: Peripheral blood smear with sickle cells (arrows)

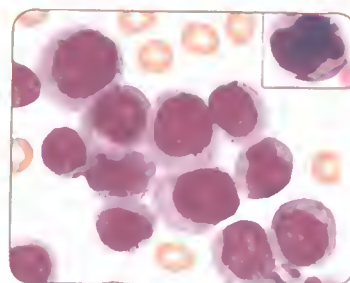
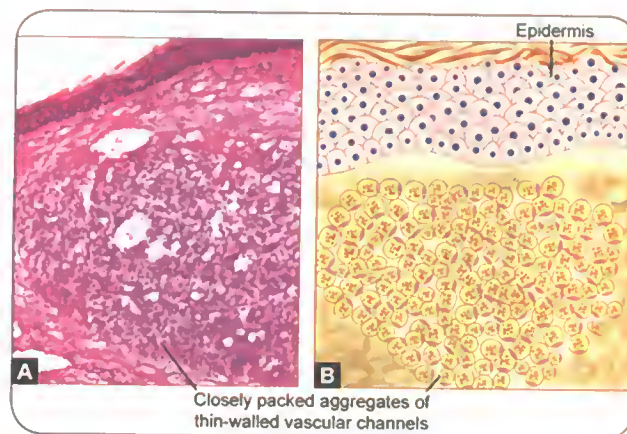
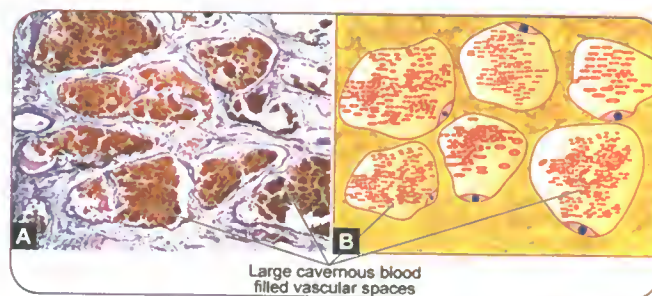


Fig. 33.61: Peripheral smear in AML with myeloblasts. Inset shows myeloblast with Auer rod



Figs. 33.62A and B: Microscopic appearance of capillary hemangioma. A. Photomicrograph; B. Diagrammatic



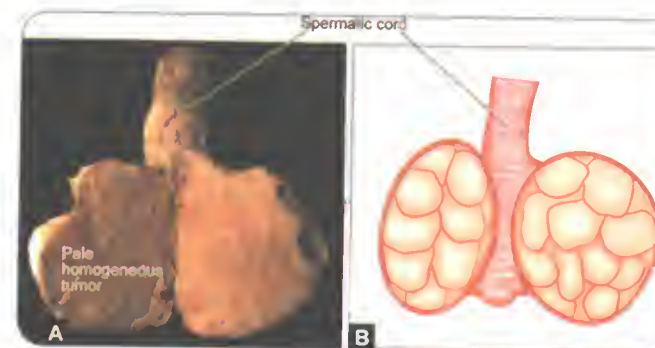
Figs. 33.63A and B: Microscopic appearance of cavernous hemangioma A. Photomicrograph; B. Diagrammatic



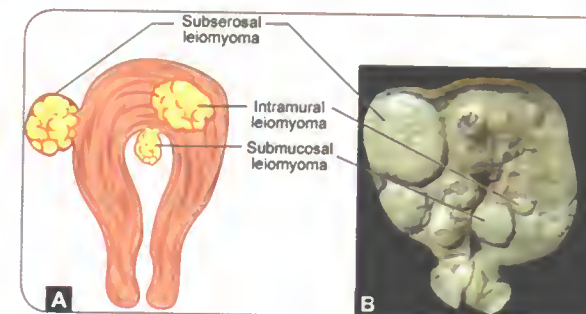
Fig. 33.64: Voluminous lung in emphysema; (A) Grossly voluminous lung with bulla on the apex of lung



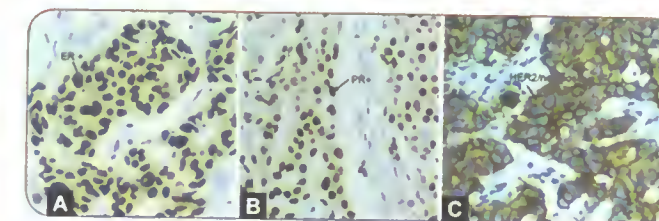
Fig. 33.65: Gross appearance of bronchiectasis with dilated bronchi and bronchioles



Figs. 33.66A and B: Gross appearance of seminoma of the testis. (A) Testis shows circumscribed, pale, fleshy, homogeneous mass; (B) (Diagrammatic) shows a lobulated tumor



Figs. 33.67A and B: A. Diagrammatic; B. Gross specimen, shows different sites of leiomyoma



Figs. 33.68A to C: Immunohistochemistry in breast carcinoma. A. ER positive; B. PR positive and C. HER2/neu positive

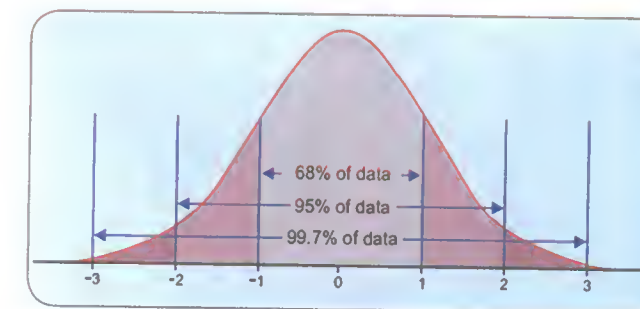


Fig. 33.69: Gaussian distribution or bell-shaped curve with mean and standard deviation (SD).



Fig. 33.70: Big space between first and second toes characteristics of Down syndrome



Fig. 33.71: Stemocleidomastoid tumor (Courtesy: Dr Ramesh Babu, government Dharpuri Medical College)



Fig. 33.72: Necrotizing enterocolitis.
(Courtesy: Dr Padmesh V)



Fig. 33.73: Infant of diabetic mother with macrosomia.



Fig. 33.74: Gastroschisis showing prolapsed bowel with no covering sac.



Fig. 33.75: Exomphalos showing prolapse of gut within an amniotic sac.

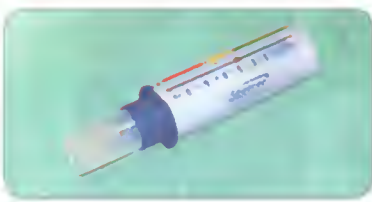


Fig. 33.76: Peak flow meter

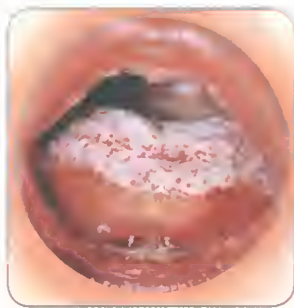


Fig. 33.77: Oral candidiasis: erythema, edema and whitish coating of mucous membranes

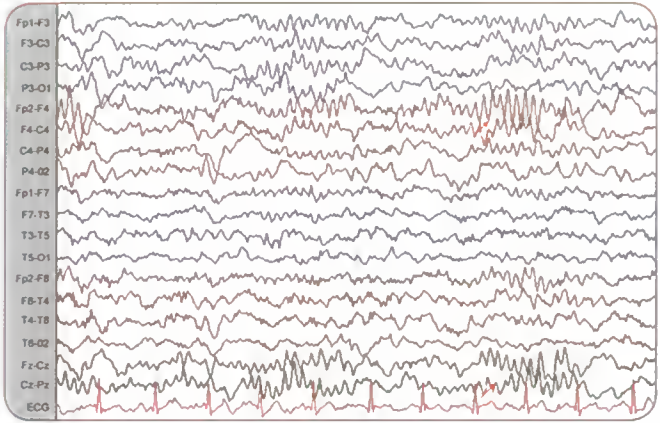
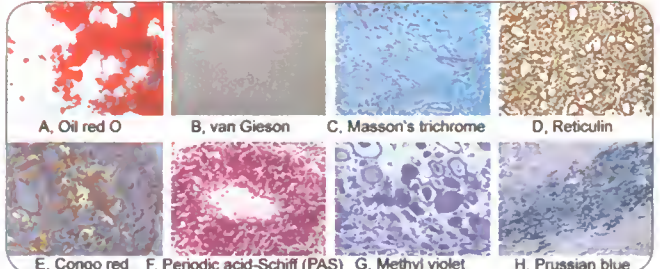


Fig. 33.78: Normal sleep EEG record showing sleep spindles (stage II non-rapid eye movement)



Figs. 33.79A to H: Common special stains. A, Oil red O for fat. B, van Gieson for collagen. C, Masson's trichrome for muscle. D, Reticulin for reticulin fibre. E, Congo red for amyloid. F, Periodic acid-Schiff (PAS) for glycogen. G, Methyl violet for metachromasia. H, Prussian blue for iron.

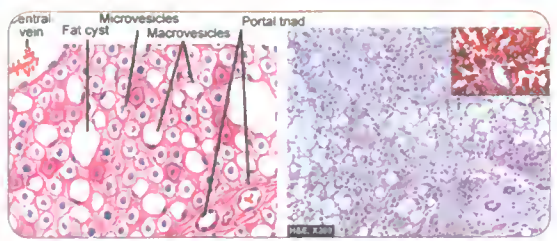


Fig. 33.80: Fatty liver. Many of the hepatocytes are distended with large fat vacuoles pushing the nuclei to the periphery (macrovesicles), while others show multiple small vacuoles in the cytoplasm (microvesicles). Inset shows red colour in the cytoplasmic fat in the hepatocytes in Oil Red O stain in frozen section.



Fig. 33.81: Dry gangrene of foot. The affected part is dry, shrunken and dark black. There is a well-delineated line of demarcation between the unaffected and affected area.

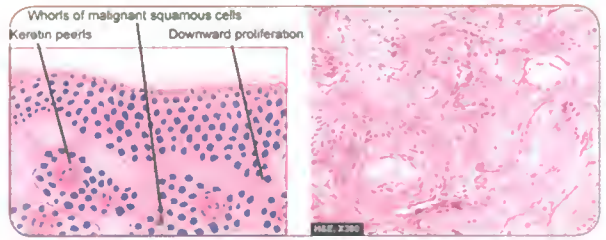


Fig. 33.82: Squamous cell carcinoma, well-differentiated. The subepithelium is invaded by downward proliferating epidermal masses of cells which show atypical features. A few horn pearls with central laminated keratin are present. There is marked inflammatory reaction in the soft tissue between the masses of tumour cells.



Fig. 33.83: Renal cell carcinoma. The pole of the kidney shows a large and tan mass while rest of the kidney has reniform contour. Sectioned surface shows irregular, circumscribed, yellowish mass with areas of haemorrhages and necrosis. The residual kidney shows compressed calyces and renal pelvis.

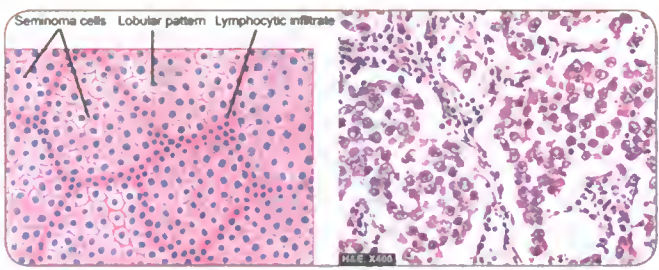


Fig. 33.84: Seminoma testis. The tumour cells are monomorphic and uniform and forming lobular pattern with lymphocytic infiltrate.

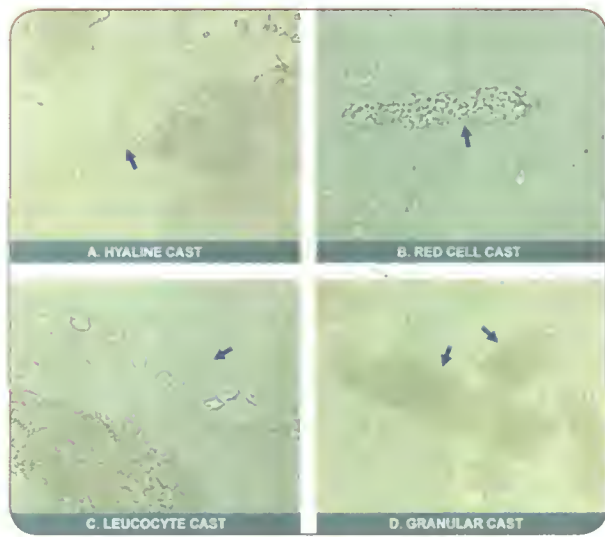


Fig. 33.85: Various types of casts in urine.

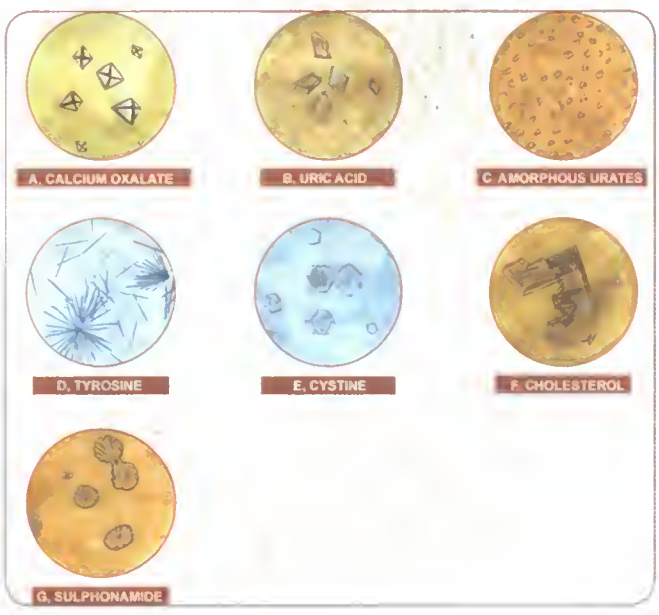


Fig. 33.86: Various types of crystals in acidic urine.

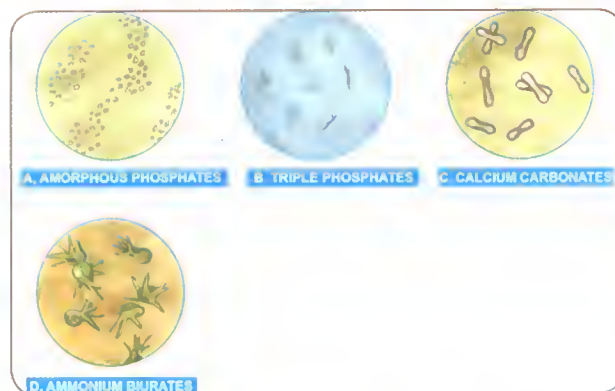
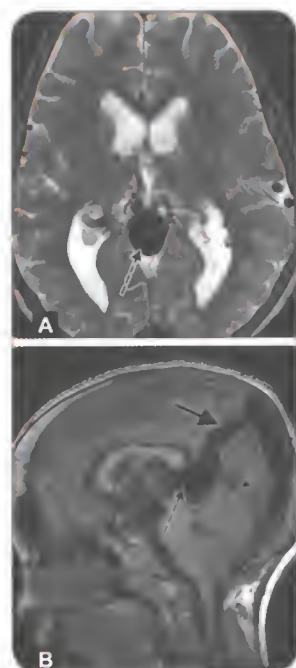
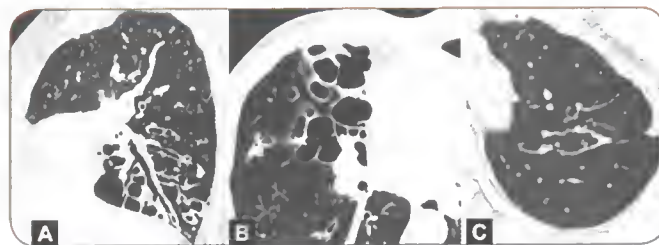


Fig. 33.87: Various types of crystals in alkaline urine.



Figs. 33.88A to B: A. Axial T2W MRI: A VGM in a 5-year-old female child. The dilated median prosencephalic vein of Markowski (dotted black arrow); B. Sagittal T1WI MR: A classic VGM. The MPV (dotted black arrow) drains via the falcine sinus (thick arrow). The straight sinus is absent (arrowhead)



Figs. 33.89A to C: A and B. Sagittal and axial HRCT image showing cystic bronchiectasis; C. Axial HRCT showing traction ectasia

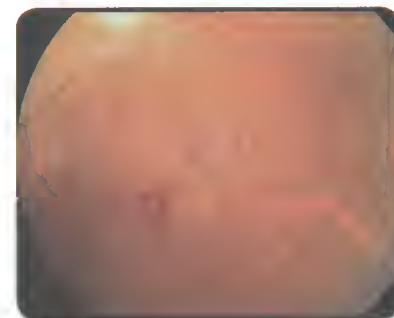


Fig. 33.90: Roth's spot—severe anemia

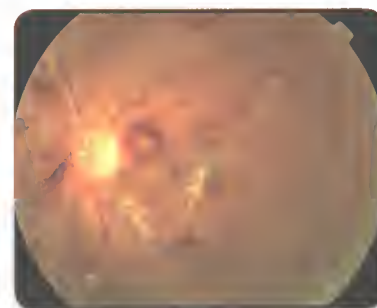


Fig. 33.91: Roth's spot with retinal hemorrhage—leukemia

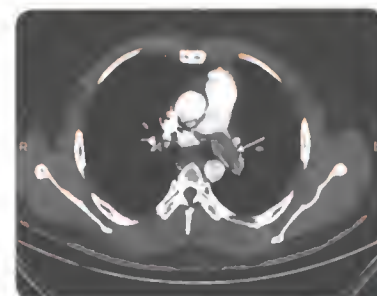


Fig. 33.92: Computed tomography pulmonary arteriography showing filling defect at the bifurcation of main pulmonary artery and in the left main pulmonary artery (arrow) suggesting thromboembolism

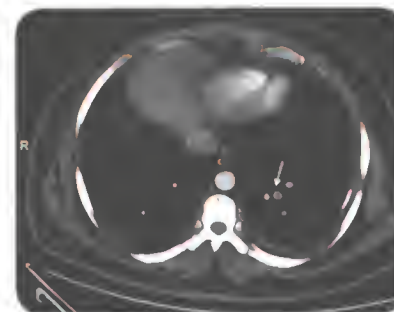


Fig. 33.93: Computed tomography pulmonary arteriography showing filling defect (arrow) in the subsegmental branches of the left descending pulmonary artery suggesting thromboembolism

Most Recent Exams Roundup

Author's Note

- This section contains one-liners of various latest 2017 entrance exams. Also, one liners from previous years' state entrance exams have been consolidated and retained since these are high yield for upcoming exams also. Any further one-liners and updates will be on the Sure Success MAGIC Facebook group - you can join at www.facebook.com/groups/suresuccessmagic.

2018 NEET PG POINTS

- Hypothyroidism** is a/w **AV block**.
- Alternative for epinephrine used in ACLS earlier was **vasopressin**.
- VMA is elevated in pheochromocytoma.
- C-wave** in JVP is due to **tricuspid bulging**.
- Drug used for prophylaxis of meningococcal meningitis is ceftriaxone > ifampicin.
- ICD (Intracardiac defibrillator) is useful in Brugada syndrome; after acute MI in coronary artery disease; in arrhythmogenic RV dysplasia.
- Pseudo-P pulmonale** is seen in **hypokalemia**.
- Diagnostic criteria for ARDS (Pg 814).
- Wallenberg syndrome** involves **PICA**.
- DMT-1** (Divalent Metal Transporter-1) facilitates entry of iron into the cell.
- Flipping effect** is $LDH1 > LDH2$ suggestive of acute MI.
- ABPA (Pg 275); Also remember that aspergillus can colonise old cavity lesions in the lung.
- NFI criteria (Pg 787).
- Neurogenic myocardial stunning is also known as Takotsubo cardiomyopathy.
- Gold criteria** for COPD (Pg 807).
- Cryoglobulinemia** is a/w Hepatitis C.
- Heller's** cardiomyotomy done for achalasia cardia.
- In **acute pancreatitis**, the **preferred** solution for rehydration/resuscitation is **isotonic crystalloid** (Ringer Lactate).
- Increased level of 5HIAA is seen in Carcinoid tumors.
- MC cause of **chronic pancreatitis** is **alcohol**.
- Feline esophagus** is a/w **Gastro-esophageal Reflux** disease (as per most gastroenterology textbooks, although H/19th says its eosinophilic esophagitis!).
- In **fasciotomy**, the layers that are opened are skin, subcutaneous tissue, superficial fascia and deep fascia.
- Chronic laxative abuse** can result in the formation of **ammonium urate** stones.
- Ideal material used for **femoropopliteal shunt** is **reverse saphenous vein**.
- False elevation of ABPI** is seen in **calcified** vessel wall.
- Abdominal aortic aneurysm** is operated when it **exceeds 5.5 cm**.
- Catgut** is absorbed by phagocytosis and enzymatic degradation.
- Massricht classification** of DCD (Donation after Circulatory Death) Donors - Pg 926.
- Rockall and Blatchford scores** are used for risk stratification in upper GI bleeding.
- Tennis racquet incision** for incising single lactiferous duct is used in **microdochectomy**.
- RET** proto-oncogene is a/w **medullary Ca thyroid**.
- Trilene** is degraded by **enzymatic degradation**.
- Struvite stone is caused by magnesium.
- The abdominal mass in pyloric stenosis in a neonate can be best palpated in epigastric area.
- Minimum interval between 2 live vaccines is **4 weeks**.
- Fontanelle last to close is anterior fontanelle.
- Dactylitis** is a/w sickle cell disease.
- Most serious and most vision threatening** neonatal conjunctivitis that can lead to blindness is **gonococcal conjunctivitis**.
- Acute PID** is a contraindication for D and C.
- MC twins after assisted reproduction is dizygotic twins.
- Drug contraindicated in PIII is **atenolol**.
- Fimbriectomy is done in the **Kroner's** method.
- Hyperprolactinemia is a/w prolactin levels above **200 ng**.
- Most common hirth related nerve palsy is **facial nerve palsy**.
- Peripartum cardiomyopathy occurs between last month of pregnancy up to 6 months postpartum.
- Establishment of feto-placental circulation is seen at 20-22 days.
- Anteversion** of uterus is maintained by round ligament.
- Torus tubaris** the tubal elevation in lateral wall of nasopharynx.

- **High tracheostomy** is done in laryngeal carcinoma.
- During acute tonsillitis, referred pain in the ear is due to **glossopharyngeal nerve**.
- Site of electrode placement in auditory brainstem implant is recess of fourth ventricle.
- Nasopharyngeal **chordoma** arises from **notochord remnants**.
- Chronic recurrent multifocal osteomyelitis is seen in **SAPHO syndrome**.
- In glaucoma, last field of vision to be lost is **temporal island of vision**.
- **Roth spots** are seen in leukemia; anemia; infective endocarditis.
- Rhino-orbital **mucormycosis** is common in diabetic ketoacidosis.
- **Cutis marmorata** is due to exposure to cold.
- **Ulnar nerve** is used for monitoring **neuromuscular blockade**.
- **Raindrop skull** pigmentation is seen in **multiple myeloma**.
- **Dream theory** of Sigmund Freud includes symbolism, condensation and displacement.
- **Sibson's fascia** is also called suprapleural membrane.
- Insulin like growth factor is secreted by liver.
- Among atypical antipsychotics, **risperidone** has maximum tendency to cause **hyperprolactinemia**.
- **Severe rheumatic chorea** is treated with **haloperidol**.
- **Anti-CD25 (IL-2 receptor)** antibody used in prophylaxis of acute organ rejection in adult patients is **basiliximab**.
- Atenolol is NOT used in the management of PHH.
- Extramammary Paget's disease is seen in **vulva**.
- Mullerian Inhibiting factor is a/w **chromosome Y**.
- Order of putrefaction: Larynx and trachea (earliest) > stomach, intestine and spleen > brain > heart > kidneys > prostate/non gravid uterus > skin, muscle, tendon > Bone.
- **Emtricitabine** has both anti-hepatitis and anti-retroviral activity.
- Earliest lesion in Crohn's disease is **aphthous ulcer**.
- Fatal lower level of BMI for **males is 13** and for **females is 11**.
- **BRAF** is a/w Papillary thyroid Ca; Hairy cell leukemia; Langerhans cell histiocytosis.
- Newly erupted teeth is covered by **Nasmyth's membrane**.
- **Maximum thermal energy** is seen in **protein metabolism**.
- **Phenylbutyrate** is used in **urea cycle disorders** since it increases renal excretion of ammonia.
- **DNA gyrase** is **topoisomerase 2**.
- MC mutation of hyper-cholesterolemia—**LDL receptor mutations**.
- Protein involved in pathology of **Lewy body dementia**—**Alpha synuclein**.
- Gene mutations in **AML** a/w favorable prognosis are **CEBPA and NPM1**.
- **ABCD1 mutation** is seen in **X-linked adrenoleukodystrophy**.
- **DAX1 gene mutation** is a/w **congenital adrenal hyperplasia**.
- Function of **acetone free methyl alcohol** in staining is that it **fixes cells to the slide**.
- **Erythropoietin** is secreted from **renal peritubular interstitial cells**.
- Tumor marker for lung adenocarcinoma is **TTF1 and cytokeratin 7**.
- **Empirical drug** for meningococcal meningitis is **ceftriaxone**.
- All ACE inhibitors are **prodrugs except captopril and lisinopril**.
- **Oliceridine** is a **CGRP** (Calcitonin Gene Related Peptide) **agonist** in clinical trials for **migraine**.
- Septic shock is NOT staphylococcal toxin mediated.
- Rhinosporidium **seeheri** is an aquatic protistan protozoa.
- Mycobacterium tuberculosis escapes immunity by **inhibition of phagolysosome fusion**.
- **Pseudomonas** is bacteria that can **contaminate disinfectant solutions**.
- **Hepatitis C** high efficacy testing in blood bank is by **NS3**.
- **Huglund deformity** is associated with **ankle**.
- **Suprachoroidal hemorrhage** is associated with **high IOP** (NOT hypotony).
- Landmark of **geniculate ganglion** in facial nerve decompression is **processus cochleariformis**.
- In a study, II patient serves as both case and control, it is called **cross over study**.
- **APML differentiation syndrome** is treated with **dexamethasone**.
- **Scorpion and jelly fish** toxins are neuro-excitatory.
- Eye is NOT involved in familial mediterranean fever.
- Pollutant released by combustion of fossil fuels that exacerbates asthma is **sulphur dioxide**.
- **Bruckenharaugh** effect is seen in **HOCM**.
- Cholecystectomy is considered completely safe in stage Ia of gallbladder carcinoma.
- MC location of congenital cyst in lung = **right bronchus**.
- **Sevoflurane** is an inhalational anesthetic that can be used **for induction**.
- Intercalated discs of cardiac muscle contain all types of cellular junctions **except** tight junctions (zonula occludens).
- **Trapezius** muscle is **triangular** in shape.
- **Injury to pubococcygeus** can lead to rectocele, cystocele and urinary incontinence.

2017 CENTRAL EXAMS NEW POINTS

- Structure between right ventricular inlet and outlet is **supraventricular crest**.
- **Vidian nerve** is related to the **floor of the sphenoid sinus**.
- **Retropharyngeal abscess** lies between buccopharyngeal fascia and alar fascia.
- Nerve passing between posterior cerebellar and superior cerebral artery is **oculomotor nerve**.
- **Vein of Labbe** drains into the **transverse sinus**.
- Maximum concentrating ability of kidney in preterm infant is **500 mOsm**.
- **Mast cell degranulation** is suggested by rise in **serum tryptase** levels.

- **Slow waves** are generated by interstitial cells of Cajal.
- **Feed forward control system** is employed during control of **temperature**.
- Human **severe combined immune deficiency** (SCID) is the most serious inherited immunological defect. Recent work has revealed defects in the predominant pathway for double-strand break repair called **nonhomologous DNA end joining, or NHEJ**.
- **Order of blood collection**. (1) Assemble equipment (needle, syringe, vacutainer tube) (2) perform handwash (3) identify and prepare patient (4) Select the site (4) Apply tourniquet 4-5 finger width above the selected venipuncture site (6) ask the patient to form a fist so that veins are more prominent (7) put on well fitting sterile gloves (8) Disinfect the site using 70% isopropyl alcohol for 30 seconds (9) Enter the vein at 30° angle (10) Once sufficient blood is drawn release the tourniquet before withdrawing the needle (11) Discard the needle and syringe (12) Check the label and amount for accuracy (13) Remove gloves and discard them
- **Neonatal CMV** is best diagnosed from **saliva > urine**.
- **Liparaahnomannan** assay is used for **Mycobacterium tuberculosis**.
- Recently confirmed viral case in India is **Crimson Congo fever**.
- **Doxycycline** is the DDC for **scrub typhus**.
- **Shunt surgery** is a **placebo** surgery.
- **Alirocumab** and **evolocumab** are **PCSK9 inhibitors**.
- Maintaining permissible hypotension to avoid bleeding is called **balanced resuscitation**.
- MC presentation of **abdominal desmoid** tumor is **abdominal mass**.
- **Functioning of the ICD tube** can be checked by seeing the movement of the air-water column during respiration.
- Test for **immediate memory**: **Serial (100-7) subtraction** test up to 5 steps.
- **Tracheostomy suction** should be limited to **10-15 seconds** at a time.
- **Trivandrum** developmental screening test is used for **0-2 years**; **Bnnadn** developmental screening test is used for **0-2.5 years (30 months)**.
- **Misophonia** is a specific dislike to certain types of sounds (e.g.: noisy chewing; loud breathing; repeated pen clicking).
- In **capnogram**, **normal beta angle is 90°** and **normal alpha angle is 100-110°**.
- **Succinate dehydrogenase** deficient **GIST** is a specific subtype of GIST in younger patients.
- Color coding of **asthma MDIs** (metered dose Inhalers): Blue for SABA; Green for LABA; Brown for ICS.
- Mutations in the **glucocerebrosidase (GBA) gene**, which encodes the lysosomal enzyme that is deficient in Gaucher's disease, are important and common risk factors for **Parkinson's disease** and related disorders.
- **Spider cells** are seen in **rhahdamyoma**.
- **Dalaglutide** is a drug used in **type 2 DM** that can be used **once weekly** at any time of the day.
- **Transferrin receptors** are maximum on **intermediate normoblasts**.
- Iron from plants is in the ferric form (Fe^{3+}); it is reduced in the intestine by cytochrome B in duodenal mucosa into reduced iron -Ferrous form (Fe^{2+}). Fe^{2+} is absorbed into intestinal mucosa by **divalent metal transporter-1 (DMT-1)**.
- The **antiarrhythmic** of choice for **local anaesthetic (bupivacaine) induced ventricular arrhythmias** is **bretyllium**.
- The **Rossmann fold** is a structural motif found in proteins that bind nucleotides, such as enzyme cofactors FAD, NAD $^{+}$, and NADP $^{+}$.
- **HEART score** for predicting major cardiac events includes: History; ECG; Age; Risk factors; initial Troponin.
- **Daroff's rule**: To detect or rule out nuclear involvement in third cranial nerve palsy.
- **Tisagenlecleucel: CAR-T cell therapy** (Chimeric Antigen Receptor T cell therapy)—uses the body's own T cells; used in B cell ALL and diffuse large B cell lymphoma.
- "**Robin Hood**" or the "**Inverse-sten**" phenomenon: Vasoconstriction caused by hypocapnia or a suitable anaesthetic agent such as **thiopentone** will cause a reduced blood flow to the normal regions of the brain resulting into redistribution or increased flow of blood to ischemic regions.

Blood therapeutic range of anti-epileptics

Drug	Therapeutic range
Carbamazepine	4-12 mcg/mL
Phenytoin	10-20 mcg/mL
Phenobarbitone	10-40 mcg/mL
Valproic acid	50-125 mcg/mL
Topiramate	2-20 mcg/mL
Ethosuximide	40-100 mcg/mL

MC in Hepatitis

MC acute viral hepatitis	HAV
MC viral hepatitis causing hepatocellular ca	HBV
MC viral hepatitis a/w transfusion	
MC viral hepatitis resulting in carrier state	
MC chronic viral hepatitis	HCV
MC sporadic acute viral hepatitis in India	HEV
MC viral hepatitis causing mortality in pregnancy	
MC glomerulopathy with HCV	Cryoglobulinemic GN > MPGN

AIIMS NOV 2016

- "Danger space" is a potential space bounded anteriorly by the *alar fascia* and posteriorly by the *prevertebral fascia*. It extends from clivus of skull above to the posterior mediastinum at the level of diaphragm. In healthy people, it is *indistinguishable from the retropharyngeal space* and is a potential path for spread of infections from the pharynx to the mediastinum.
- Control Centre for *stapedial reflex* is *superior olivary complex*.
- *Extra-embryonic* mesoderm is derived from *primary yolk sac*.
- Anterior 2/3rd of tongue is demarcated from posterior 1/3rd by *sulcus terminalis*.
- In *Sjogren's syndrome*, salivary gland output is *low*. Resting salivary secretion < 0.1 ml. min and stimulated salivary secretion < 0.7 ml/min are seen. Other *findings in saliva*: Increased sodium, IgA, anti-Ro and anti-La antibodies; Increased lactoferrin, beta-2 microglobulin, PGE2, lysozyme, thromboxane B2, IL-6 and hyaluronic acid (NONE of these is specific enough to be used as a marker).
- Endocochlear potential = + **80 mV**
- *HCN*-gated channels have a role in *cardiac rhythm* generation.
- MMC in gut appears at intervals of **90 minutes**.
- Vitamin synthesized in vivo in the body by humans = *Niacin*.
- The CG island is a short stretch of DNA in which the frequency of the CG sequence is higher than other regions. It is also called the CpG island, where "p" simply indicates that "C" and "G" are connected by a phosphodiester bond. The CG sequences in inactive genes are usually *methyalted* to suppress their expression.
- A *common intermediate* in the synthesis of all steroid hormones is *pregnenelone*.
- Stain useful for identifying pre-malignant lesion of the lip is *toluidine blue*.
- *Linagliptin* can be given safely in *renal failure*.
- Risk of *lactic acidosis due to metformin* is increased in: hypotensive states; CVS disease; Respiratory disease; hepatic failure; renal failure; alcoholics; advanced age.
- *Coxiella burnetii* is an obligate intracellular pathogen.
- *St. Anthony's fire* is due to poisoning by *ergot alkaloids*.
- Characteristic *ascending paralysis* is a/w poisoning by *conium (hemlock)*.
- MC used lens in indirect ophthalmoscopy is **+20D** lens.
- Hypereosinophilic syndrome is a/w persistent eosinophilia > **1500/mm³**.
- *Parabronchial* diverticulum is a *true* diverticulum of esophagus.
- Dose of *misoprostol* to control bleeding in *PPH* is **600 micrograms/day**.
- Correct sequence in *Maslow's hierarchy* of needs is physiological needs = safety - belonging - self esteem - self actualization.

AIIMS MAY 2016

- The hormone with a permissive action at the onset of puberty is *Leptin*.
- *Pre-Botzinger complex* is the site of respiratory *rhythm* generation.
- Best index to measure cardiac afterload is *mean arterial pressure*.
- In the mammalian genome, maximum number of genes code for the receptors of *odorants*.
- Best fixative for testicular tissue is *Bouin's fluid*.
- Strong indicator of *humoral rejection* is *C4d*.
- Most potent reactive oxygen species/free radical is *Hydroxyl (OH⁻)*.
- *RBCs* should be transfused within 4 hours of issue from blood bank with **18-20G needle**.
- *CYP450* inhibition is *least* by *Rabeprazole*.
- Transfusion-associated malaria has a shorter incubation period because of presence in the blood of trophozoites.
- *Gaenslen's test* is used to detect *sacroiliac joint* dysfunction.
- The most widely used test to measure aqueous tear deficiency is the Schirmer's test. An alternative test is the *Phenol Red thread* test—wherein a special cotton thread impregnated with phenol red is placed in the conjunctival sac for 15 seconds—the thread which is pH-sensitive turns color from yellow to orange indicating the length of the thread wetted by tears.
- Immediately after PDT (photodynamic therapy), the color of the lesion changes to *white*.
- Important methods of *inventory control* include *ABC* (A-most valuable; C-least valuable) analysis and *VED* analysis (Vital - Essential-Desirable).
- *Torniquet* test (capillary fragility test) is used in daily follow-up patients with *Dengue* virus.
- *Sacral agenesis/caudal regression* syndrome is almost *pathognomonic* of *diabetic embryopathy*.
- In infant of diabetic mother—*MC* congenital anomaly is *cardiovascular*—in that *VSD* is MC; TGV is most specific cardiac anomaly.
- *Double bleb sign* on ultrasonography is depictive of *amniotic sac and yolk sac*.

MHCET 2016

- The nerve carrying taste sensation from the circumvallate papillae is *Glossopharyngeal*.
- The layer of the scalp that is known as 'dangerous area of scalp' is *loose areolar tissue*.
- The peripheral proteins attached to the integral proteins function almost entirely as *enzymes*.
- *Poiseuille's law* is $F = (PA - PB)\pi r^4 / 8\eta L$.
- *AV nodal delay* is 0.1 second.
- A *photoelectric flame photometer* is a device used in inorganic chemical analysis to determine the concentration of certain metal ions, among them sodium, potassium, lithium, and calcium

- The *Cockcroft-Gault* equation allows the creatinine clearance to be estimated from the serum creatinine
- *Ras gene* is a growth promoting marker
- *Speckled pattern* of immunofluorescence is seen in anti-Sm antibody
- *Subepithelial cambium layer* is seen in *rhabdomyosarcoma*.
- *Larva currens* is a/w *Strongyloides stercoralis*.
- In contrast associated Acute Kidney Injury the serum creatinine usually peaks within **3-5 days**.
- Second Wednesday of October every year has been designated as '*World Disaster Reduction Day*'.
- *Global-Hunger Index* includes child underweight; child mortality and proportion of under nourished population.
- The twelfth five year plan 2012-2017 stresses on long-term objective of establishing *universal health coverage*.
- World population is expected to reach **8 billion** by **2025**.
- Resistance to more than one first line anti tuberculosis drug (other than both isoniazid and rifampicin) is called as *polydrug resistance*.
- Goal 5 of 'Millennium Development Goals' is related to - *maternal health*.
- *Hinchey classification* is used in cases of complicated diverticulitis.
- In Wilson's disease, hepatic copper content usually *exceeds 250 ig per gram dry weight*.
- According to *Quintero staging* system: Development of fetal hydrops in recipient twin in twin to twin transfusion syndrome belongs to stage IV.
- Sonographic diagnosis of *polyhydramnios* is made if a largest vertical amniotic fluid pocket is more than **8 cm**.
- In post menopausal bleeding, endometrial thickness *more than 4 mm*. by transvaginal sonography is an indication for (D & C) Dilatation and Curettage.
- '*Bear claw*' appearance on contrast enhanced CT scan abdomen is seen in *hepatic laceration*.
- Latent strabismus is termed as *phoria*.
- *PANSS* is a psychiatric rating scale for assessment of *psychotic disorders*.
- Individuals with *Williams-Beuren Syndrome* are at increased risk of expressive language disorder.

COMEDK 2016

- Commonest nerve injury involving Monteggia fracture is *posterior interosseous nerve injury*.
- *Ferryman-Gallaway scoring* system is used for hirsutism.
- *Anderson Tawil syndrome* is a potassium channelopathy.
- *Fish tailing* is seen in stab wound.
- *Gail model* is used to assess relative risk for breast cancer.
- During surgery, *Couley's pointer* is a landmark used to identify facial nerve.
- *Hot tub lung* caused by mycobacterium avium complex.
- *Leptin* prevents obesity.

- The cofactor required for the enzyme alcohol dehydrogenase is *zinc*.
- The wave length of femtosecond laser is **1053 nm**.
- The copper T 380A intrauterine device can be inserted *within 3.5 days* of unprotected intercourse for 100% effective emergency contraception
- Intracranial bleeds in premature infants is seen in the *germinal matrix*.
- Mediastinal shift in tension pneumothorax may be absent if associated with *consolidation*.

APPG 2016

- As per Consumer Protection Act, if the complaint involves amount of ₹ 20-100 lakh, the case has to be filed with state commission and if more than ₹ **100 lakhs**, with the *national commission*.
- Chronic mountain sickness DOES NOT produce hyperventilation
- During Dilatation & Curettage, if there is perforation during sounding, one should *monitor pulse and BP*.
- *Grenz or Bucky ray therapy* helps in treatment of unresponsive scalp psoriasis
- Mission Indradhanush
- Mission Indradhanush was launched by Ministry of Health and Family Welfare (MOHFW) Government of India on 25th December, 2014.
- The objective of this mission is to ensure that all children under the age of two years as well as pregnant women are fully immunized with seven vaccine preventable diseases.
- The Mission Indradhanush, depicting seven colours of the rainbow, targets to immunize all children against seven vaccine preventable diseases, namely:
 - Diphtheria
 - Pertussis (Whooping Cough)
 - Tetanus
 - Tuberculosis
 - Polio
 - Hepatitis B
 - Measles.
- In addition to this, vaccines for Japanese Encephalitis (JE) and Haemophilus influenzae type B (HIB) are also being provided in selected states.
- The ratio of radiation delivered in an *abdominal CT scan* compared to a chest radiogram is **500:1**.
- Crouzon syndrome does NOT present with a large anterior fontanelle
- *High glycolytic capacity* is characteristic of type II skeletal muscle fibres
- *Cricovocal membrane* is an intrinsic laryngeal membrane.
- *Coxiella Burnetti* may survive the Holder method of Pasteurisation
- *IV vancomycin* is ineffective in *C. difficile* diarrhea since the bacteria remains within the colonic lumen and does not invade the mucosa (oral vancomycin is very effective).

- The theme of **World Health Day** celebrated on 7th April 2015 was "from farm to plate, make food safe".
- Among patients with polymyositis, **anti-Jo-1** is associated with an increased risk of interstitial lung disease
- **Popliteus** is **intracapsular** in origin.
- **Tirofiban** is GpIIb/IIIa antagonist

WBPB 2016

- **Pleocercoid** larvae are a/w *D. latum*.
- **Mesangial proliferative** GN is the MC type of GN a/w *visceral leishmaniasis*.
- **Hot cross bun sign** on MRI refers to appearance of the pons in neurodegenerative diseases like multisystem atrophy; spinocerebellar atrophy types 2 and 3; variant CJD.
- Excessive sex desire in males is **satyriasis**
- **Trefoil peptides** in the gastric mucosa protect it from autodigestion.
- **Jerk test** is used for posterior shoulder dislocation.
- **Lifespan of a mosquito** varies from 8-34 days; normally an adult mosquito lives for about 2 weeks.
- **Chronic subdural hemorrhage** was called as pachymeningitis hemorrhagica interna
- **Stallworthy sign**: Slowing of fetal heart rate on pressing the head down I to the pelvis and prompt recovery on release of pressure; this sign is suggestive of **posterior placenta praevia**.
- **Cingulum** is a type of **long association fibre**.

AIIMS MAY 2015

- Cranial nerve **nucleus** lying **beneath the facial colliculus** is nucleus of **abducent nerve**.
- The only cranial nerves that transmit **general visceral efferent (parasympathetic)** fibres are Oculomotor N; Facial N; Glossopharyngeal N and Vagus N. (**III, VII, IX and X**).
- **Mesorectal fascia** (fascia propria) contains - superior rectal artery, superior rectal vein and its branches, lymph nodes and branches from inferior mesenteric plexus.
- **Microvilli** are NOT present in **collecting duct**.
- **Primary oocytes** are arrested in **prophase-I (dictyotene)** before birth
- **Assortment of maternal and paternal chromosomes** takes place at the stage of **primary to secondary spermatocyte**.
- A **50% increase in radius** of vessel will cause **rise in blood flow by 5 times**.
- The clot formed is not stable unless **extensive cross linking** occurs that is done by **factor XIIIa**.
- **ABO system** of blood grouping is an example of **codominance**.
- **Amylin** (islet amyloid polypeptide) is a 37-amino acid peptide synthesized and secreted primarily in the **beta cells** of the pancreatic islets together with insulin.
- **Brown adipose tissue** is mainly found **around the kidneys, adrenal glands, between the scapulae, in axilla, along the spinal column and around the blood vessels of the neck, mediastinum and loin. Subcutaneous fat is white**.

- **Thiamine deficiency** can cause **lactic acidosis** due to **dysfunction of pyruvate dehydrogenase**
- Enzyme used for **both glycogenesis and glycogenolysis** is **phosphoglucomutase**.
- **RNA interference (RNAi)** is a means of silencing genes by way of **mRNA degradation**. **Gene knock down** by this method is achieved by introducing small **double-stranded interfering RNAs (siRNA)** into the cytoplasm.
- **Cre (Cause recombination) recombinase** is a 38 kDa enzyme isolated from the P1 bacteriophage. It efficiently **binds to loxP sites**.
- **Oil Red O** (Lipid Stain) is used for the histological visualization of fat cells and neutral fat in fresh **frozen tissue** sections.
- **MC nephropathy** a/w **malignancy** is **Membranous nephropathy**.
- In **flow cytometry**, **forward scatter** is directly related to **cell size** and **side scatter** to **granularity**.
- **Beta-3 receptors** are located on adipose tissue and their stimulation causes **lipolysis**.
- Despite the small surface area for absorption, certain drugs which are **non-ionic and highly lipid soluble** are effectively absorbed **sublingually** -hence the drugs **nitroglycerin and buprenorphine** are administered by this route.
- **Vibrio cholerae** acts by disrupting **tight junctions**.
- Section **416 CrPC** - Postponement of capital sentence on pregnant woman: If a woman sentenced to death is found to be pregnant, the High Court shall commute the sentence to imprisonment for life.
- **Fragmentation or segmentation** (trucking or shunting) of the **blood columns (Kevorkian sign)** in the **retinal vessels** appear within minutes after death, and persists for about an hour.
- India's **age of consent for sex is 18 years** under the **Criminal Law (Amendment) Act, 2013**.
- **Kashima operation** is done for **vocal cords**
- When compared to blood, **vitreous humor** has high concentration of **ascorbate**.
- **MC route of spread of retinoblastoma** is **through the optic nerve**.
- **Long ciliary nerve**, a branch of **nasociliary nerve**, that is a branch of **ophthalmic division of trigeminal nerve** supplies the **cornea**.
- **Multifocal ERG** assesses **macular cone function**.
- **ABCG2** is a **universal marker of stem cells** and also a **limbal epithelial stem cell marker**.
- High molecular wt proteins in human **cataractous lens** are **HIM3 and HIM4**.
- "**Nikshay**" is a newly launched central government software is used for tracking **TB cases**.
- **FSSAI** under **MOHFW**.
- **Haddon matrix** is related to **injury prevention**.
- Best product to be given in **multiple clotting factor deficiency** and active bleeding = Fresh Frozen Plasma (**FFP**)
- Best **non-invasive** investigation to check for **viable myocardium** is **PET**.

- **Mallory Weiss** syndrome mainly affects **left gastric artery**.
- **Incision preferred** for **diaphragmatic surgery** is **circumferential**.
- In a patient with **thrombocytopenia** the target platelet count after platelet transfusion to perform an invasive procedure is 50,000/microL.
- **Ventriculo-peritoneal** shunt (VP shunt) is the MC procedure for **hydrocephalus**.
- For **esophageal cancer**, **prognosis** is determined by **T stage**.
- **MC and acceptable** method of **bariatric surgery** is **roux en Y procedure**.
- The Oncotype Dx breast cancer test and **Manumaprint** are genotyping test intended for **stage I or II, node negative, ER positive**.
- **Carbetocin** standard dose: **100 micrograms (1mL) by IV** injection, immediately post-delivery by Caesarean section and preferably prior to removal of placenta.
- **Propofol** causes **pain on IV** administration.
- "**Judet**" view of X-ray is for **pelvis**.
- **Shenton line** is seen in X ray of **hip**.
- **Inv of choice** for **acute appendicitis** in children is **USG**.
- **Inv of choice** in **stress fracture** is **MRI**.
- **Inv of choice** for **biliary atresia** in a 2 month old is **hepatic scintigraphy** (technetium-labeled diisopropyl iminodiacetic acid (**DISIDA**) nuclear scintiscan)
- Best method to know the **integrity of Implantable Cardioverter Defibrillator** is to do **plain X-ray** (MRI and CT are contraindicated).
- **Rat hole** is a/w **intermediate range firearm** injury.
- **Jersey finger** is caused by rupture of **avulsion of the flexor digitorum profundus tendon**; it is the MC type of closed rupture and is caused by a **sudden hyperextension injury during active flexion**; ring finger MC affected.
- **Cancellous bone** is the **most metabolically active** part in the bone.

MHCET 2015

- The amino acid which does NOT allow the formation of alpha-helix is **Proline**.
- The RNA involved in production of correct 3' ends of Histone mRNA is **snRNA**.
- In development of language, a child is able to **tell stories by 4 years**.
- **Angiofollicular lymph node hyperplasia** is **Castleman disease**
- **Tissue Harmonic imaging** involves use of **sound waves**.
- **Subarachnoid space** extends till **S2 vertebra**.
- The **half life of cesium** is **30.07 years**.
- **Receptor Concept** was first introduced by **John Newport Langley**.
- The Monoclonal antibody directed **against CD20**, used in treatment of Rheumatoid arthritis is **rituximab**.
- Children with **Thalassemia and Iron overload** are at an increased risk for infection with **Yersinia Enterocolitica**.

- **Normal Apgar Score** with **Acidosis** in a neonate is seen in **High Fetal Catecholamine levels**.
- Cutoff level of **Waist-Hip Ratio** in women indicating **abdominal fat accumulation** is **0.85**.
- Serotypes of **Polio virus** is most commonly associated with **vaccine associated paralytic poliomyelitis** is **serotype 3**.
- **IIHH syndrome** is caused by defect in **Ornithine Permease**; HHH = Hyperornithinemia-Hyperammonemia-Homocitrullinuria.
- Throughout the country every year **anti malaria month** is observed during the month of **June**.
- **Amyloid Light chain (AL)** is derived from **Plasma cells**.
- **Cytosolic Cytochrome C** plays an important function in **Apoptosis**.
- **Monkey facies and Baggy pants** refers to look in **Marasmus** because of loss of fat
- **Monochorionic-Monoamniotic** twin occurs if **division occurs > 8 days**.
- The name of following procedure which includes, the excision of the prolapsed rectum and associated sigmoid colon from below, & construction of a coloanal anastomosis is the **Altemier's procedure**.
- Types of **anal fistula** includes intersphincteric, trans-sphincteric, suprasphincteric extrasphincteric primary tracks is called as **Park's classification**.
- Drug used in **opioid induced constipation** is **Alvimopan**.
- **Ross** classified five stages of **death** (response to death).
- **Wilson's disease** is caused by defect in **ATP 7B mutation**.
- Ratio of stroke volume output to compliance of arterial tree approximately determines **pulse pressure**.
- In Integrated Disease Surveillance Project in India, **presumptive diagnosis** is done by **PHC Medical Officer**.
- For the **prevention of human rabies**, immediate **flushing and washing the wound (s)** in animal bite cases, with plenty of soap and water, under running tap should be carried out for **15 minutes**.
- In the **partogram**, the credit of the concept of Alert line and Action line goes to **Philpott**.
- **Serum Lithium level** should be **checked earliest after 5 days** of constant dosing
- **Priapism** is a strong **predictor of severe cord injury** even in intubated patients.
- **PGE2** is **elevated** in **hypothalamic tissue** during **fever**.
- Marker for **Langerhans cell histiocytosis** is **CD1a**.
- **Nephrotic range proteinuria** is defined as protein excretion of more than **40 mg/m²/hr**.
- Premature fusion of coronal, sphenofrontal and frontoethmoidal sutures is seen in **Turriccephaly (Oxycephaly, Tower-like skull)**
- **Ochsner-Sherren** regimen is used in management of **appendicular mass**.
- The **food standards in India** are based on the standards of the **codex alimentarius**.
- **Natural (living) ligature of uterus** is **myometrium**.

- In *modified radical neck dissection Type I*, the structure which is *preserved* is *sphenal accessory nerve*.
- **DASH** = Dietary approaches to stop hypertension
- **Molecular Policeman** = **p53**.
- As per International Commission of Radiation Units and measurements Report No. 38: **High dose Brachytherapy** is **12 Gy/hr**.

WBPGRMAT 2015

- **Myotonic dystrophica** is due to gene defect on **chromosome 19** (DMPK gene).
- **Gemellus inferior** nerve supply is by **nerve to quadratus femoris**.
- **Pulmonary ligament** formed by **mediastinal pleura**.
- MC bone tumors of the hand = **enchondromas**.
- Pathognomic of **motor neuron disease** = **fasciculations** (rpt from AIIMS 2009)
- For osteoporosis T score, hip bone mineral density is used.
- **Hair cells located at the base** of the **basilar membrane** are most excited by **high-pitched tones**, whereas hair cells at the **top (apex)** of the basilar membrane are excited by **low pitched tones**.
- **Radiation induced necrosis** diagnosed by **PET scan** (rpt from AIIMS 2009)
- Risk of **Coronary heart diseases** is **same as non-smokers after 15 years** of quitting smoking
- **DNA polymerase** catalyzes the formation of the **phosphodiester bond** which makes up the backbone of DNA molecules. It uses a **magnesium ion** in catalytic activity to balance the charge from the phosphate group.
- **Irish's node** is an **enlarged left axillary lymph node** in **gastric Cancer**.
- **Scirrhus carcinoma of stomach** diagnosed by **double contrast barium meal**.
- **Radio-frequency Surgery** is an **atraumatic method of cutting and coagulation** soft tissues. **No pressure** is needed and the cells are vaporized in the path of the radiowaves, causing them to split apart. This results in **less trauma to the cells, less fibrous scarring and less postoperative discomfort** than typical removal with a scalpel (Pressureless cutting & pinpoint coagulation without any damage to surrounding tissue) — this results in excellent cosmetic results without scarring & rapid healing.
- **Autosomal-dominant myotonia congenita** (Thomsen Disease) caused by reduced sarcolemmal **chloride conductance** due to mutations in **CLCN1**.
- Swedish professor **Tage Malmstrom** developed the **ventouse**, or **Malmstrom extractor**.
- **Parotidectomy incision** is **S shaped**.
- Deficiency of **lysosomal acid lipase** causes 2 distinct phenotypes in humans: **Wolman disease** and **cholesteryl ester storage disease**.
- **DNA polymerase gamma** is the only known DNA polymerase in human mitochondria and is **essential for mitochondrial DNA replication and repair**.
- **Thermogenin** (now known as **uncoupling protein 1, or UCP1**) is an uncoupling protein **found in the mitochondria of brown adipose tissue**. It is used to generate heat by non-shivering thermogenesis.
- The word "**pathology**" comes from the **Greek** words "pathos" meaning "disease" and "logos" meaning "a treatise" — a treatise of disease.
- In **1905, Schaudinn and Hoffmann** discovered the causative agent of syphilis - **Treponema pallidum**.
- Disease that is called the '**father of public health**'—**cholera**.
- **Pentoxifylline** is the **best known and most widely investigated drug with rheological action** (increases blood flow through narrow vessels).
- A hallmark of chickenpox is that all stages (red bumps, blisters, and scabs) can appear on the body at the same time.
- The WHO guidelines state that, in **hospital wards, noise levels** should **not exceed 30 dB LEq** (day and night) and that **peak noise levels at night** should not exceed **40 dB**.
- Andersen cascade, Sieve sampler and the **Reynier's slit Sampler** are used to determine aerosol concentrations of bacteria (**air conditioner air contamination**).
- According to **Sphere guidelines**, in case of disasters, there should be **one tap for 250 people** and **one hand pump for 500 people**.
- **Persistent, symptomatic macroglossia** involving the **intrinsic muscles of the tongue** may require **reduction glossoplasty**.
- **Volume of eye 6.5 ml**, Volume of adult = 30 ml; weight of adult eyeball = 7 grams.
- **Iris is thickest 2 mm** from pupillary margin and **thinnest at its root** where it attaches to the anterior ciliary body.
- **MC site of pressure sore** in paraplegia = **ischium**
- **15% of inguinal hernias** are **bilateral**
- Women with a mutation in the **BRCA1 gene**, located on **chromosome 17**, have an estimated **85% chance of developing breast cancer** in their lifetime.
- The **Intermediate syndrome** following **organophosphorus (OP) insecticide poisoning** comprised characteristic symptoms and signs occurring **after apparent recovery from the acute cholinergic syndrome**. As the syndrome occurred after the acute cholinergic syndrome but before organophosphate-induced delayed polyneuropathy, the syndrome was called '**intermediate syndrome**'.
- Transfusion of packed red blood cells (RBCs) provides **1 mg per ml—transfused of additional elemental iron; i.e., 1 unit packed red cells = 250 mg iron**.
- The **normal range of INR** for a healthy person not using warfarin is **0.8–1.2**, and for people on **warfarin therapy** an INR of **2.0–3.0** usually targeted.

TNPG 2015

- **Hepatic artery** supplies **30% of liver**.
- **Inferior ganglion of the vagus nerve** = **nodose ganglion**.

- The reference range for **prothrombin time** is **9.5–13.5 seconds**.
- Minimum concentration of **hCG** at which **gestational sac** is visible in **transvaginal U/S** = **1500 mIU/ml**.
- **Fetal heart sounds** are seen by **transabdominal U/S** at **6 weeks**.
- To identify a **cervical ectopic pregnancy**, cervical glands must be attached to the placenta, the placenta must be implanted below the place where the uterine vessels reach the uterus and the attachment between the placenta and the cervix should be intimate. These conditions are known as **Rubln's criteria**.
- **Velocardiofacial syndrome**, the most frequent known interstitial deletion found in humans (22q11.2 deletion), is associated with high rates of psychiatric disorder, particularly **schizophrenia**.
- **Vagus nerve stimulator (VNS)** is approved for the long-term treatment of chronic or recurrent **depression** which has not responded to usual treatments.
- **Incisura** in aortic trachea—refers to beginning of isovolumic relaxation and **closure of aortic valve**.
- A **tingible body macrophage** is a type of macrophage predominantly found in germinal centers, containing many phagocytized, apoptotic cells in various states of degradation, referred to as tingible bodies (tingible meaning stainable). Tingible body macrophages contain condensed chromatin fragments. Characteristic of **reactive follicular hyperplasia** of the lymph node.
- **Chronic pain** transmission: **Paleo-spinothalamic tract**
- **Brown staining** of teeth is due to **chlorhexidine**.

APPG 2015

- **Nylon sutures** are nonabsorbable monofilament **polyamide** sutures.
- **Fastform bacteria** show **gliding** motility.
- **Modified New York City medium** for culture of **Neisseria gonorrhoeae**.

ESSENTIAL INFO FROM OTHER EXAMS

- **Ilathazar score** is for CTSI (**CT severity index**) of **acute pancreatitis**
- **World Health day** is on **April 7**
- MC type **moluscum contagiosum** virus causing **skin infection** and **most prevalent type** is **MCV-1**.
- **Marble bone** disease is **Osteopetrosis**.
- **Keshan's disease** is due to **deficiency of selenium**.
- **Superior mesenteric artery syndrome** is a rare complication in patients immobilized in a body cast or **hip spica** - "**cast syndrome**" (following **spinal surgery**).
- **Ehrlichiosis**: DOC is **doxycycline**.
- **Accessory obturator artery** arises from **inferior epigastric artery**.

- Small joint spared in **rheumatoid arthritis** is **distal interphalangeal joint**
- **Jackson staging system** is used for **Cauls**.
- **CURB 65 score** for **pneumonia** includes: **Confusion**, blood urea nitrogen, **Respiratory rate** and **systolic BP**.
- **Angel dust** is name given for **phencyclidine**
- **Schaffer's sign** in **retinal detachment** consist of **anterior vitreous pigments (tobacco dusting)**.
- **Whiff test**. Several drops of a potassium hydroxide (KOH) solution are added to a sample of vaginal discharge to see whether a **strong fishy odor** is produced for **bacterial vaginosis**.
- **Lorenzo's oil** is used in **adrenoleukodystrophy**
- **MC site of dermatofibrosarcoma** is **trunk**
- **Best flap** for **total nasal reconstruction** is **forehead flap**.
- **Sphacellular Ataxia type 7** a/w **retinal pigmentary disturbance** is type 7.
- MC site of **ischemic colitis**—**splenic flexure**
- MC tumor arising from **thyroglossal cyst** - **papillary Ca**.
- **Chocolate cyanosis** - **methemoglobinemia**
- MC affected nerve in **sarcoidosis** - **VII cranial nerve**.
- **Body volume index (BVI)**: BVI system automatically measures BMI, waist circumference and waist-hip ratio in addition to highly sophisticated 3D volumetric and body composition analysis.
- **Ergometrine** derived from **Claviceps purpurea**
- **John Snow** used a **spot map** to show cases of **cholera** were **centred around the public water pump**.
- **Sildenafil (Viagra)** should NOT be combined with **nitrates** because of risk of large hypotension
- "**Unsolved**" fracture—**intracapsular fracture neck of femur**.
- **Forgotten tendon** of rotator cuff - **subscapularis**
- **Fasudil** is a potent **Rho kinase inhibitor** and vasodilator used in relieving cerebral vasospasm in **subarachnoid hemorrhage**; treating **pulmonary hypertension** and improving **cognitive function** in **Alzheimer's disease**.
- As the **use of refrigeration for preserving foods** has increased around the world, the rates of **stomach cancer** have declined.
- Four main stages (**Escobar's pathological stages**) of **Neurocysticercosis**: vesicular (no host reaction); colloidal vesicular (most symptomatic stage); granular nodular; **nodular calcified (no edema)**.
- As per WHO recommendations—eye care infrastructure should have **20 centres of excellence**; **200 training centres**; **2000 service centres** and **20000 primary level vision centres**.
- **Acamprosate** is an anti-alcoholic agent. It is used to prevent the need for alcohol in people who have stopped drinking alcohol.
- **Ocrlplasma** is a recombinant protease for releasing **vitreomacular adhesion**.
- **Burns in children** - **Lund and Bowder** scale.
- **Tetralatine** is given **subcutaneously**.
- **Crumpled tissue paper** cells—**Gaucher's disease**

- **Lixapitan, toltrapitan, and satrapitan** are oral selective vasopressin-2 receptor antagonists.
- **Pruritus** is caused by **poison of Spanish fly**.
- **Suicide enzyme, cyclooxygenase**.
- **Lerapimale** is drug of choice for **steroid resistant nephrotic syndrome**.
- **Methods of placental separation: Mathew Duncan's method** (beginning from leading edge) and **Shultz method**.
- **French paradox:** situation in France is paradoxical in that there is **high intake of saturated fat but low mortality from CHD**.
- **Charcot-Marie-Tooth disease** is the MC type of hereditary neuropathy.
- **NNK, NNN and polonium 210** are carcinogens specific for tobacco related oral cancer.
- Cough persisting for **more than 8 weeks** is called **chronic cough**.
- **Kenaury's sign:** venous hum over **epigastric region in portal HTN**.
- **Glaister keen rod** is used for grading of **hymenal tear in a victim of rape**.
- **SEC 228A IPC** = Punishment for disclosure of rape victim.
- In 2008, a series of suicides planned over the internet in Japan came to be known as **The Japanese Detergent Suicide technique** which involves mixing toilet cleaner and bath salts to create **hydrogen sulfide gas (rotten eggs odour)**.
- **Rofecoxib** was withdrawn due to increased **cardiac mortality** (acute MI and stroke).
- **Amylin** is co-released with insulin by **beta cells of pancreas** and may act as an inhibitor of insulin.
- Increased incidence of **neonatal jaundice is with ventouse delivery** (due to increased cephalhematoma).
- **Olfactory neuroblastoma**, also called **esthesioneuroblastoma** or **esthesioneuroepithelioma** is a malignant neuroendocrine neoplasm that arises from the **olfactory mucosa**.
- Two types of artificial foot for below knee amputees are **SACH** and **SAFE**:
 - The simplest type of non-articulated foot is the **SACH** (solid ankle-cushion heel) foot. The heel is rigid. Ankle action is provided by the soft rubber heel which compresses under load during the early part of the stance phase of walking. The rubber heel wedges are available in three densities: soft, medium, and hard.
 - The **SAFE** (solid ankle-flexible-endoskeletal) foot has the same action as the SACH plus the ability for the sole to conform to slightly irregular surfaces and thus makes it easier for the amputee to walk over uneven terrain. Feet of this type make walking easier because of the flexibility, and are sometimes called "flexible keel" feet.
- **Prader-Willi syndrome:** Low muscle tone, short stature, incomplete sexual development, cognitive disabilities, problem behaviors, and a chronic feeling of hunger that can lead to excessive eating and life-threatening obesity (**high ghrelin levels**).
- **Houston's valves:** On the mucosal (lumen) aspect of the rectum, 3 curves are marked by semicircular folds called Houston's valves, these valves **DO NOT** contain all muscle layers; they are an excellent place to perform rectal biopsy since minimal risk of perforation; they are **NOT** present after mobilization of the rectum.
- **Rounded atelectasis:**
 - Occurs as a consequence of diseases with chronic pleural scarring, especially asbestosis-related pleural disease and TB; Most often at the lung bases, posteromedially; Must be subpleural in position; It is asymptomatic **BUT** important because it resembles a bronchogenic carcinoma
 - Imaging Findings:
 - Rounded density at lung base
 - Contiguous to area of pleural disease or superimposed on apparent asbestosis-related pleural disease or TB
 - **Comet tail on CT:** vessels and bronchi converge upon and appear to swirl around mass
 - **Crow's feet** — linear bands radiating from mass into lung parenchyma
 - Linear densities radiate back toward hilum
 - May have air bronchogram.
- **Docosahexaenoic acid (DHA):** is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. DHA is present in fatty fish (salmon, tuna, mackerel) and mother's milk.
- **Thiopentone** decreases CNS metabolism and reduces ICP; also reduces cerebral blood flow by cerebral arterial vasoconstriction - cerebroprotective effect.
- **Temozolamide** is an oral alkylating agent used for treatment of **grade IV astrocytoma** (glioblastoma multiforme).
- **Vibrio alginolyticus** can cause **otitis externa** and wound infection.
- Exposure to **misoprostol** in first trimester is a/w **Moebius syndrome**.
- **Kegel's exercises** are pelvic floor exercises for strengthening the **pubococcygeus** muscle; can be started **during pregnancy itself**.
- **Stress induced cardiomyopathy** is also called **broken heart syndrome**, **apical ballooning syndrome**, **neurocardiogenic shock** or **takotsubo cardiomyopathy**.
- When a posterior inferior cerebellar artery (**PICA**) **aneurysm** ruptures, the patient may present with hemorrhage restricted to the posterior fossa or the cerebellum.
- **Keratin** in nails has more **disulfide bonds**—hence lesser flexibility compared to fewer disulfide bonds in hair and skin.
- **Ritonavir** use is a/w **hypertriglyceridemia**.
- **Flaps in back pain**
- **Foramen transversarium** is found only in the **cervical vertebrae**.

- **Critical closing volume** is the volume above the residual volume at which the small airways begin to collapse. **Closing capacity** is the sum of residual volume and closing volume.
- A **genetic code** in which some amino acids may each be encoded by more than one codon is called **degeneracy**.
- In lesbianism: Active partner = **dyke** or **butch**; passive partner = **femme**.
- **Last organ** to be dissected during autopsy in **asphyxia death** is the **neck**.
- **Fixative** used in histopathology is most commonly **buffered neutral 10% formalin**.
- People with **Bombay blood group** have a **lack of A, B and H antigen on RBC**.
- **Irreversible cell injury** shows **amorphous density in mitochondria**.
- Among the antiglaucoma drugs, **timolol** has been suspected to cause **nasolacrimal duct obstruction**.
- "Natural" supplementary therapies for heart failure include **Myrohanan (terminalia arjuna)** and **Co-enzyme Q10 hawthorn extract**.
- **Splino cerebellar ataxia type 2 (SCA2)** has been reported as the commonest dominant hereditary ataxia in **India**.
- **Ilagen Poisenille** principle is the basis for thermadilution method used in measurement of **cardiac output by pulmonary catheter**.
- **Reactivation of HSV-1 infection** causes "**fever blister**" (also called **Cold sore**; **Oral herpes simplex**; **Herpes labialis**).
- The **benefits of reperfusion therapy** in acute myocardial infarction is confined to the **first 12 hours** after symptom onset.
- **MULIBREY Nanism** = Muscle Liver Brain Eye + Constrictive pericarditis; Also growth failure and mesodermal anomalies.
- **Dural ectasia** is seen in **Marfan's syndrome**.
- Overall, **MRI** is the **most helpful** diagnostic tool in monitoring **spinal tuberculosis** and the treatment.
- **Russell Viper venom test** is done for **recurrent abortion**—for detection of **lupus anticoagulant**.
- **APT test: Swallowed blood syndrome** refers to bloody stools passed on the 2nd or 3rd day of life. The blood may be swallowed during delivery or may be from a fissure on the mother's nipple. The APT test is used to differentiate swallowed blood syndrome from infant GI hemorrhage or blood from mother. The test can be done on feces or vomitus. Test result will indicate whether blood present in feces/vomitus is of fetal (alkali resistant HbF) or maternal origin.
- **Vestibular Evoked Myogenic Potential (VEMP):** is an otolith mediated short latency reflex that occurs in response to intense auditory stimuli and is recorded using **sternocleidomastoid electromyography**. Clinically VEMP is useful in **detecting superior semicircular canal dehiscence**, in determining **integrity of inferior vestibular nerve** and can be used to assess **otolith function**.
- Modified Bell's staging system is used for necrotizing enterocolitis - details in surgery chapter.
- **Laryngoscopy** is a **two handed procedure**—In a right handed person, the handle of the laryngoscope is held in the left hand leaving the right hand free to position the patient and to insert the endotracheal tube.
- **Bracket like intracranial calcification** is seen in **lipoma of corpus callosum**.
- **Fluphenazine** is available as a **depot** preparation.
- **Pheochromocytomas** have a classic appearance on MRI—appearing as an adrenal mass showing iso-intense signal on T1-weighted images and high signal described as "**light bulb**" bright on T2-weighted images.
- **Size E** gas cylinder is commonly used on the **anesthetic machine**.
- **Rivastigmine** is used for dementia a/w **Alzheimer's disease and Parkinson's disease** also.
- While draining ischioanal abscess if the inferior rectal nerve is cut, it may result in anal incontinence due to loss of function of the external anal sphincter.
- **Plain catgut** is derived from **submucosa of jejunum of sheep**.
- **Increased mitochondrial outer-membrane permeability** is the major trigger of the **intrinsc apoptosis pathway**.
- **VACTERL** = Vertebral defects, Anal atresia, Cardiac defects, Tracheo-esophageal fistula, Renal anomalies, and Limb abnormalities.
- **CHARGE** = Coloboma, Heart defect, Atresia choanae (also known as choanal atresia), Retarded growth and development, Genital abnormality, and Ear abnormality.
- **Drugs for MRSA** treatment = doxycycline or trimethoprim with rifampicin or fusidic acid (rifampicin and fusidic acid should NOT be used together due to risk of jaundice); linezolid; nitrofurantoin for UTI by MRSA.
- Safer drugs for treating **TB during pregnancy and lactation** are **isoniazid, rifampicin and ethambutol**.
- **Diffuse axonal injury (DAI):** A shearing type of **brain injury** seen in severe **head trauma**. The cut end of axons appear as "**retraction balls**"; these represent egress of excess cytoplasm from at end of axons.
- **Guyon's tunnel:** contains ulnar nerve and artery; it is a depression between the pisiform and hook of hamate.
- **Insulin sensitizing agents** used in **polycystic ovary syndrome** include metformin, rosiglitazone, pioglitazone and D-chiro-inositol.
- **Levosimendan** is a **calcium sensitizer** used in the management of acutely decompensated congestive heart failure. It increases the sensitivity of the heart to calcium, thus increasing cardiac contractility without a rise in intracellular calcium. Levosimendan exerts its effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner. It also has a vasodilatory effect, by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation.

- **Waldeyer's fascia** is the **presacral fascia**.
- **CD71** mesangial IgA1 receptor is expressed more in **IgA nephropathy**.
- Detection of **virulence marker antigen (VMA)** by **ELISA** is done to detect virulence in **Shigella and EHEC**.
- Wilms tumor **WT1 gene** - located on chromosome **11p13**.
- **Thiamine deficiency** can be assessed by checking **RBC transketolase levels**.
- Serum normally contains slightly more **LDH2** than **LDH1**. An **LDH1 > LDH2** is called a **"flipped LDH"** pattern. Seen in **acute myocardial infarction**.
- The **adrenal cortex** develops from **mesoderm**. The **adrenal medulla** develops from **neural crest**.
- The **indusium griseum** is a thin layer of grey matter which covers the **superior surface of the corpus callosum**.
- **Scaphocephaly** or **boat skull** is the **most common** form of cranial deformity in **craniosynostosis** - results from premature closure of the sagittal suture.
- **Plagiocephaly** refers to **asymmetric flattening of the calvarium**.
- **Glottic cancer** with **fixed vocal cords** is **stage 3**.
- The **lyre sign** refers to the splaying of the internal and external carotid by a **carotid body tumour**.
- **Puberphonia** ("Mutational falsetto" and "Voice break") is the persistence of an unusually **high pitched voice even after puberty** in the absence of organic causes; commonly seen in **males**. This condition is **best treated by voice therapy called GUTZMAN'S pressure test**. In this the person is asked to speak with the thyroid prominence being pressed backwards and downwards to relax the overstretched cords and to produce low tone voice. Also **Type III phonosurgery** can be done which includes surgical shortening and relaxation of cord.
- In **small cell carcinoma of lung**, blood vessels in necrotic area may show smudged hematoxophilic material in their walls, which represents DNA released from tumour cells. This is referred to as **Azzopardi effect**.
- **Tanaka giant cell** - A **lipid-laden histiocyte** in which multiple nuclei are grouped around a small island of cytoplasm. Seen in **fat necrosis, xanthoma, xanthogranuloma and dermatofibroma**.
- **Kanavel's Four Cardinal Signs** is used for diagnosing **infectious tenosynovitis**.
- Transfusion related acute lung injury (TRALI): Acute (within 1-6 hrs) blood transfusion complication characterized by - **noncardiogenic pulmonary edema** with hypoxemia (< 90% oxygen saturation), dyspnea, tachypnea, fever and hypotension. **Multiparous female blood donors** are likely to harbour various paternally derived **antileukocyte antibodies** that subsequently target host neutrophil specific epitopes or HLA class I or II antigens. **Pulmonary vascular sequestration of neutrophils** with leucopenia occurs. CXR shows fluffy alveolar infiltrates; cardiomegaly and pleural effusions are absent.
- **Tombstone iliac bones** and **trident hand** are seen in **achondroplasia**.
- **Transplacental spread of carcinoma** from mother to fetus: **malignant melanoma (MC)**; also with Ca breast and lung.
- **Antibiotics** are used in **guttate psoriasis**.
- **Nephelometry** is a test to quickly and **accurately measure the specific level of immunoglobulins** in blood - specifically **IgM, IgG, and IgA**.
- **Aconite** is also called **mitha hishi**.
- Normal **post menopausal endometrial thickness** is about **2-4 mm**. Higher thickness indicated endometrial tumors.
- For smoking cessation, nicotine replacement therapy is first choice. Non nicotine products are **hupropan** and **varenicline**.
- **Carbon monoxide (CO) poisoning** occurs frequently in victims of **enclosed space fires**, resulting in the formation of **carboxyhemoglobin (COHb)**.
- **Vibroacoustic stimulation** is the application of a vibratory sound stimulus in the abdomen of a pregnant woman to **induce FHR accelerations**. The presence of FHR accelerations reliably predicts the absence of fetal metabolic acidemia.
- **Sirtuins** belong to family of histone deacetylases. Mammals possess **seven sirtuins (SIRT1-7)**.
- Their functions are intimately related to the metabolism of nicotinamide adenine dinucleotide (NAD), a coenzyme used as an oxidizing or reducing agent in a variety of essential metabolic processes. SIRT1 is a putative target of **resveratrol**, which is thought to activate the enzyme and, therefore, might **enhance lifespan** and, presumably **healthspan** as well.
- **Ropinirole** is **drug of choice for restless legs syndrome**.
- Biologically, **DNA ligases** are essential for the joining of **Okazaki fragments** during replication, and for completing short-patch DNA synthesis occurring in DNA repair process.
- **Pure-tone average (PTA)** is the average of hearing sensitivity at 500, 1000, and 2000. This average should approximate the speech reception threshold (SRT), within 5 dB, and the speech detection threshold (SDT), within 6-8 dB.
- **Torus aorticus** is the prominent region of the right atrial septum sited superiorly and anteriorly. It is superior to the coronary sinus and anterior to the fossa ovalis. It represents the deeper and anterior surface of the posterior sinus and cusp of the aortic valve.
- The **Van Nys Index** is a classification and grading system for **DCIS** that is useful in therapeutic planning. Applying the criteria of **tumor size, margin width (margin clearance) and pathologic classification (nuclear grade)**, points are scored that predict the risk of tumor recurrence.
- **Breuer Lockhart reflex** is **laryngospasm** caused by lighter plane of anesthesia.
- **Myotonic dystrophy** pathology: **type I fibre atrophy, central nuclei, sarcoplasmic masses, ring fibres** (ringbinden).
- **"Latch" Mechanism** for Prolonged Holding of Contractions of **Smooth Muscle**: muscle maintains its full force of contraction despite reduced amount of continuing excitation and lesser energy is required for comparable sustained skeletal muscle

- contraction (as low as 1/300). The importance of the latch mechanism is that it can maintain prolonged tonic contraction in smooth muscle for hours with little use of energy.
- **Largest protein** in muscle that connects M line and Z line = **titin**.
- **"Swajal Dhara"** was launched on 25th December, 2002, to open up the reform initiatives in the rural drinking water supply sector throughout the country. **Swajaldhara 2 district** is the unit for implementation.
- If the bony presenting part of the fetus is at the level of the ischial spines, it is called **zero station**.
- **Omalizumab** is a recombinant humanized **IgG1 monoclonal anti-IgE antibody** that binds to the IgE molecule. **Omalizumab (subcutaneous injection)** IS INDICATED FOR adults and adolescents (12 years of age and above) with **moderate to severe persistent asthma** who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. NOT useful in status asthmaticus.
- **Velcro crepitations** are heard in **interstitial lung disease**.
- **Autonomic dysreflexia** is a syndrome of massive imbalanced reflex sympathetic discharge occurring in patients with spinal cord injury **above the sacral sympathetic outflow (T5-T6)**.
- **Circumcision** is **contraindicated in hypospadias** as the foreskin is necessary as donor tissue during surgical repair.
- **Frenkel's exercises** are a series of motions of increasing difficulty performed by ataxic patients to facilitate the restoration of coordination.
- Classification systems for gastric adenocarcinomas are: **Lauren**; WHO classification; **Mug** classification; **Japanese** classification; **Barrmann's** (macroscopic - polypoid/fungating, ulcerating with raised borders, ulcerative infiltrating and diffuse infiltrative).
- **Chandler Index** gives the average number of **hookworm** eggs per gram of feces for the entire community - < 200 (not much significant); 200-250 (potential danger); 250-300 (minor public health problem); > 300 (major public health problem).
- **Posterior femoral muscles** are supplied by the perforating branches of the **profunda femoris artery**.
- **Femoral sheath** does NOT contain the femoral nerve.
- **Pneumoperitoneum** is best diagnosed by **plain X-ray abdomen**.
- Most **dangerous type of pneumothorax** is **tension pneumothorax**.
- Most **dangerous urinary catheter** is **male metal catheter**.
- **Capsule endoscopy** is used in diagnose **occult GI bleeding**.
- According to **Glasgow coma scale** the best predictor of neurological outcome is **motor score**.
- **Topical retinoids** in acne treatment: **adapalene, tretinoin, tazarotene**.
- **Dentigerous cyst** arises from the area around the crown of an unerupted permanent tooth.
- **Evening primrose oil** is used in the treatment of **cyclical mastalgia**.
- The **Lever's shunt** is performed in **ascites**.
- The treatment of choice for **postnatal depression** is **fluoxetine**.
- **Powder burn spots** over pelvic viscera is seen in **endometriosis**.
- **Infantile whiplash syndrome** is **battered baby syndrome**.
- UNICEF's **GPI FFF program** stands for = Growth monitor log, Oral rehydration, Breast feeding, Immunization, Female education, Female spacing and Female supplements.
- **Metal fume fever** is caused by **zinc oxide** inhalation.
- Treatment of **gastric antral vascular ectasia (GAVE, watermelon stomach)** is by **endoscopic argon laser plasma coagulation**.
- Source of **bleeding in duodenal ulcer** is **gastrooduodenal artery**.
- Route of administration of antibiotics in bacterial **endophthalmitis** is **intravitreal**.
- **Cartwheel appearance** of tympanic membrane is seen in **acute suppurative otitis media**.
- **Multislice CT** has had the most dramatic impact in imaging the **liver**.
- There are 5 flexor tendon **zones of the hand** - **zone 2** is often called **"Bunnell's No Man's land"**.
- **Road to health** chart was designed by **David Morley**.
- **Idazoxan** is an **alpha-2-antagonist**.
- **Tree bark appearance** in vessel wall is seen in **sypilis**.
- **Fetal middle cerebral artery Doppler** is most useful in the evaluation of **fetal anemia**.
- **Spinal metastases** from **kidney** is NOT radiosensitive.
- **Iliac tumor MC** occurs in lower 1/3 of ureter.
- The most readily detected **clinical sign of hypermagnesemia** is **disappearance of deep tendon reflexes**.
- **Haemorrhagic meningitis** is caused by **Bacillus anthracis**.
- **Thermactinomyces sacchari** is the causative agent of **Bugassosis and Farmer's lung**.
- **Thymoglobulin** is a **polyclonal antibody**.
- The **commonest cause of death in ARDS** is **non-pulmonary organ failure**.
- **Increased Rouleaux formation** in the peripheral blood is a characteristic feature of **multiple myeloma**.
- **Nodular scabies** is found in **scrotum**.
- **Theory of contagion** was first enunciated by **Fracastorius**.
- The **sacrospinous ligament** is the degenerated tendon of **long head of biceps femoris**.
- **Indian Evidence act** was enacted in **1872**.
- **Brain sand** = **corpora arenacea** = calcium containing salts in **pineal gland**.
- **Askin tumor** = primitive neuroectodermal tumor (pNET) of the chest wall in young adults and adolescents.

- **Greenhouse effect (global warming):**
 - It is due to emission of greenhouse gases (CO_2 **most commonly**, ozone, CFC-chlorofluorocarbons, halons, methane and N_2O) into the atmosphere. Responsible for increase in average global surface temperature; **NOT seen** with N_2 .
- **Onion bulb appearance on nerve biopsy** is a classic finding of **Dejerine-Sottas Syndrome**
- **Intranasal endoscopic approach** can be used for **lacrimal gland, optic nerve decompression and pituitary gland**.
- **Raloxifene** currently approved only for the prevention and **treatment of osteoporosis in postmenopausal women**.
- **Mechanisms of methotrexate resistance:**
 - RFC dysfunction
 - DHFR (dihydrofolate reductase) amplification or mutation
 - Decreased FPGS activity
 - Increased GGH (gamma glutamyl hydroxylase) activity.
- **Ramelteon**, selectively binds to the MT1 and MT2 receptors in the suprachiasmatic nucleus, instead of binding to GABA-A receptors, such as with drugs like zolpidem, eszopiclone, and zaleplon; Used for treatment of sleeplessness.
- Treatment of **overactive bladder**: **Darifenacin; solifenacin; fesoterodine; tolterodine; oxybutynin; trospium chloride; propiverine**.
- CD marker specific for myeloid series is CD117.
- **Lift-off test** is done for **isolating subscapularis injury**. The test is performed by passively internally rotating the arm behind the back and off the patient's spine. A positive test occurs when the examiner releases the maximally internally rotated arm, and it falls to the patient's back. A weak test result is observed when the patient can maintain the position of maximal internal rotation but is unable to apply resistance to the examiner's hand.
- Posterior glenohumeral instability is tested by **jerk test**.
- **Velpeau and sling-and-swathe bandage** is used for shoulder dislocations, proximal humeral fractures and humerus fractures.
- **Rosen T-10 protocol** (high dose methotrexate) - for osteosarcoma.
- **Enteroviruses** are the **MC cause of meningoencephalitis**.
- The **twin peak sign on ultrasonography** indicates the presence of a **dichorionic-diamniotic twin gestation** (multiple gestation).
- Parasitic infection (echinococcus, **hydatid cyst**) **are the MC cause of splenic cysts**.
- **Bismuth-Strasberg classification** is used for **biliary tract trauma**.
- Trauma Score - Injury Severity Score: **TRISS = RTS + ISS + Age**.
- **Grayhack shunt** is between corpora cavernosa & saphenous vein used for treatment of **priapism**.
- **Prenatal diagnosis of hemophilia** is done by **linkage analysis**.
- **Arden index** is related to **EOG**.
- **Primary impact injuries** are seen on **legs**.
- Marker of **Langerhans Cell Histiocytosis** is **CD1a**.
- **Prof Erich Mülle** of Germany, performed the first **laparoscopic cholecystectomy** in 1985.
- **Fluorescence recovery after photobleaching (FRAP)**: This technique is very useful in biological studies of cell membrane diffusion and protein binding; Movement of protein from nucleus to cytoplasm can be seen by FRAP.
- **Reflex hallucinations** occurs in **Synaesthesia**.
- Variant of **Giant cell tumor** is **Non ossifying fibroma**.
- "**Cardiac polyp**" is Usually a rounded thrombus attached to the endocardium.
- The purpose of the '**Dial Test**' is to diagnose **posterolateral instability**.
- Lift off test is used to diagnose subscapularis rupture.
- **Children's Hospital Eastern Ontario Pain Scale (CHEOPS)**: (recommended for children 1-7 years old) - a score greater than 4 indicates pain. Criteria to observe includes: cry, facial expression, child talking/verbal, torso (active/inactive), touch (touching the area), legs (moving or restrained).
- **Kaplan-Meier method**: the Kaplan-Meier method is a nonparametric (actuarial) technique for estimating time-related events (the survivorship function). It ordinarily is used to analyze death as an outcome. It may be used effectively to analyze time to an endpoint, such as remission.
- Anatomical snuff box contains **radial artery**.
- **Modafinil** is an analeptic drug approved for the treatment of narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea.
- **Porins** are beta barrel proteins that cross a cellular membrane and act as a pore through which molecules can diffuse. Unlike other membrane transport proteins, porins are large enough to allow passive diffusion, i.e., they act as channels that are specific to different types of molecules. They are present in the outer membrane of Gram-negative bacteria and some Gram-positive bacteria of the group Mycolata, the mitochondria, and the chloroplast.
- **Aquaporins**: Water crosses cell membranes by two routes: by diffusion through the lipid bilayer and through water channels called aquaporins.
- **STEP**: who is promoting the use of the stepwise approach to enable countries to set up surveillance systems for NCD risk factors
- The movement at the following joint permits a person to look towards the right or left - **atlantoaxial joint**.
- The first costosternal joint is a synarthrosis.
- The articular cartilage is **devoid of perichondrium**; it is a **vascular** accounting for the low capacity for repair and it **lacks the capacity to regenerate**. It has **no nerve supply** that is the reason there is pain only when the bone comes into contact in a case of arthritis.
- The **Coulnaud's segmental nomenclature** is based on the position of the **hepatic veins and biliary ducts**.

- The cell junctions allowing the exchange of cytoplasmic molecules between two cells are called - **gap junctions**.
- The cells belonging to the following type of epithelium are provided with extra reserve of cell membrane—**transitional**.
- The **middle cardiac vein** is located at the posterior interventricular sulcus.
- The blood vessel related to the **paraduodenal fossa** is **inferior mesenteric vein**.
- The **commonest variation** in the arteries arising from the arch of aorta is left common carotid A arising from the brachiocephalic trunk.
- **Y chromosome** is **acrocentric**.
- **Alpha and beta helix** pleated sheets are examples of **secondary structure**.
- The following groups of proteins assist in the folding of other proteins—**Chaperones**.
- The transmembrane region of a protein is likely to have a stretch of **hydrophobic amino acids**.
- The following can be a homologous substitution for valine in hemoglobin—**Isoleucine**.
- Symptoms of **sucrase deficiency** are the same as that of **lactase deficiency**.
- **Shine Dalgarno sequence** in bacterial mRNA is **near AUG** codon.
- A segment of eukaryotic gene that is not represented in the mature mRNA is known as **Intron**.
- The enzyme associated with the conversion of androgen to estrogen in the growing ovarian follicle is **aromatase**.
- **Selenium** is known to influence the body's ability to handle oxidative stresses.
- The **buffering capacity** of a buffer is **maximum** at **pH equal to pKa**.
- **Gel filtration chromatography** separates protein molecules based on their **molecular size**.
- The transformation of half of the molecules of an optically active enantiomer (pure isomer) into molecules which possess exactly the opposite (mirror image configuration) with resultant complete loss of rotatory power became of statistical balance between equal numbers of dextro and levo rotatory molecules is called **racemisation**.
- Oxidation of odd chain fatty acids produces propionyl CoA.
- The protein rich in **basic amino acids**, which function in the packaging of DNA in chromosomes, is **histone**.
- **RFLP** is used for analysis of **chromosome structure**.
- The main enzyme responsible for activation of **xenobiotics** is **cytochrome P 450**.
- Porphobilinogen in urine produces pink colour with Ehrlich's aldehyde reagent.
- **Sleep spindles** and **K complexes** are found in **stage 2 NREM** sleep.
- The **parvocellular pathway** from lateral geniculate nucleus to visual cortex is most sensitive for the stimulus of: **color contrast**.
- The fibers from the contralateral nasal hemiretina project to the following layers of the lateral geniculate nucleus: Layers 1, 4 and 6.
- The **MC cause of tricuspid regurgitation** is secondary to **dilatation of right ventricle**.
- **Whole blood of 1 unit** will raise the hemoglobin by **1gm%** in an average size adult.
- In neuroblastoma, the expression of the neurotrophin receptor **TRK A** is highly correlated with **favorable biology** (localized disease) whereas TRK B is associated with advanced stage disease.
- **Memory T cells** can be identified using the following marker - **CD45RO**.
- Raised serum levels of **lipoprotein-a** is a predictor of **atherosclerosis**.
- **IgM** is the earliest immunoglobulin to be synthesized by the fetus beginning at about **20 weeks** of age.
- The most sensitive method for detecting *Chlamydia trachomatis* infection is **direct fluorescent antibody test**.
- The most appropriate method for collecting urine for culture in a case of vesicovaginal fistula is **Foley's catheter**.
- Antiprogesterone compound RU 486 (mifepristone) is effective for inducing abortion if the duration of pregnancy is **upto 63 days** (9 weeks).
- Hunter's operation involves ligation of an artery in proximal side of an aneurysm above the first collateral.
- **Pseudoclaudication** is due to **compression of cauda equina**.
- Aseptic loosening in cemented total hip replacement occurs as a result of hypersensitivity response to **high-density polythene debris**.
- When any motion of body produces disturbance and motion related artifact in images in radiology or during radiotherapy, then **gating** is done to **reduce the motion related artifacts**.
- The **catheter materials** most suited for **long-term use** is **silicone**.
- Adulterants of heroin include lactose and fruit sugars, quinine, powdered milk, phenacetin, caffeine, antipyrine and strychnine.
- Maximum density of goblet cells is seen on the **inferonasal** surface of the bulbar conjunctiva.
- Neonates and infants with **Downs' syndrome** may have a condition known as **myeloproliferative syndrome** which mimics congenital leukemia.
- **Multicystic dysplastic kidney** is the **MC cause** of an abdominal mass in the newborn.
- The neonatal kidney achieves concentrating ability equivalent to the adult kidney by the age of **2 years**.
- An **elevation of HbA2** (2 alpha-globin chains complexed with 2 delta-globin chains) demonstrated by **electrophoresis or column chromatography** confirms the **diagnosis of beta thalassemia trait**—gold standard.

- The ***lac operon***:
 - Lac is an ***operon*** required for the transport and metabolism of lactose in *Escherichia coli* and some other enteric bacteria. It consists of three adjacent structural genes, a promoter, a terminator, and an operator.
 - The lac operon is regulated by several factors including the availability of glucose and of lactose.
 - Gene regulation of the lac operon was the first genetic regulatory mechanism to be elucidated and is often used as the prototype example of ***prokaryotic gene regulation***.
 - ***CAP*** (catabolite activator protein, also called CRP – cAMP receptor protein) in LAC operon is Positive regulator; repressor is the negative regulator.
- All endothelial cells produce thrombomodulin except those found in cerebral microcirculation.
- **Fordyce** spots (granules) in oral cavity arise from **sebaceous glands**.
- The temperature at which entire magnetic system must be maintained is about **4 degree Kelvin** for superconduction.
- The superconducting material used in magnet of MRI is NbTi
- **Bosentan** is an **endothelin receptor antagonist**.
- Co-administration of **indinavir** should be avoided with ATT (**rifampicin** particularly). Rifampicin induces cytochrome P450 activity and reduces blood concentrations of indinavir.
- Photodynamic therapy is used in the treatment of wet **ARM D** (age related macular degeneration). **Verteporfin** dye and **diode laser** is used.
- **Information Technology Act** was passed by the Government of India in **2000**.
- Transplantation of **Human Organs Act** was passed by Government of India in **1994**.
- Gas which is used in **MRI for cooling** is **helium**.

Index

The 'Detailed Index' and 'Topic wise index' of all chapters will be uploaded on the author's Facebook group (www.facebook.com/groups/suresuccessmagic) and can be downloaded from there in PDF format.